UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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ROTASHIELD™ ROTAVIRUS VACCINE

SPONSOR PRESENTATION

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OPEN SESSION

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FRIDAY

DECEMBER 12, 1997

The meeting of the Advisory Committee was held in the Versailles Ballroom at the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, at 9:30 a.m., Dr. Patricia Ferrieri, Committee Chair, presiding.

PRESENT:

DR. PATRICIA FERRIERI Chair

DR. ADAORA ADIMORA

DR. CAROLINE HALL

DR. KATHRYN EDWARDS	
REBECCA COLE	
DR. MARY ESTES	
DR. CLAIRE BROOME	
DR. HERBERT DuPONT	
DR. THOMAS FLEMING	
DR. NEAL HALSEY	
DR. DAVID KARZON	
DR. YVONNE MALDONADO	
DR. JOHN MODLIN	
DR. DIXIE SNIDER, Jr.	
NANCY CHERRY	Exec. Secy.

ALSO PRESENT:

DR. ROGER GLASS	
DR. KATHRYN CARBONE	FDA
DR. LARAINE HENCHAL	FDA
DR. JOSEPH CAMARDO	Wyeth-Ayerst
DR. PETER PARADISO	
DR. JOHN PETRICCIANI	
DR. MARGARET RENNELS	
DR. MAUREEN SKOWRONEK	

C O N T E N T S

P R O C E E D I N G S

9:33 a.m.

OPEN SESSION

CHAIRPERSON FERRIERI: Good morning. I'd like to call to order the Open Session. We're here to discuss the RotaShield™ rotavirus vaccine. I thought we would begin by introducing our panel at the table, and then Ms. Cherry will have some administrative announcements.

Dr. Snider, would you mind starting again?

DR. SNIDER: Dixie Snider, Associate Director for Science, Centers for Disease Control and Prevention.

DR. EDWARDS: Kathy Edwards, Department of Pediatrics, Vanderbilt University.

DR. HALL: Caroline Hall, professor of Medicine and Pediatrics, University of Rochester.

DR. FLEMING: Thomas Fleming, Chair, Biostatistics, University of Washington.

DR. ESTES: Mary Estes, professor of Molecular Virology, Baylor College of Medicine.

MS. COLE: Rebecca Cole, Consumer Representative, Chapel Hill, North Carolina.

DR. ADIMORA: Adaora Adimora, assistant professor of Medicine, Infectious Diseases, UNC,

Chapel Hill.

CHAIRPERSON FERRIERI: Patricia Ferrieri, professor of Laboratory Medicine and Pathology in Pediatric Infectious Diseases, University of Minnesota Medical School, Minneapolis.

DR. KARZON: David Karzon, Emeritus professor of Pediatrics and Microbiology at Vanderbilt Medical Center.

DR. DuPONT: Herbert DuPont, professor of Medicine and Infectious Diseases at Baylor College of Medicine and the University of Texas in Houston.

MR. MODLIN: I'm John Modlin, professor of Pediatrics and Medicine at Dartmouth Medical School.

DR. MALDONADO: Yvonne Maldonado, associate professor of Pediatrics, Stanford University, and member of the National Vaccine Advisory Committee.

DR. HALSEY: Neal Halsey, professor in International Health and Pediatrics at Johns Hopkins University, and chair of the Committee on Infectious Diseases for the American Academy of Pediatrics.

CHAIRPERSON FERRIERI: Thank you very much. Back to Ms. Cherry.

MS. CHERRY: This announcement is made a part of the record at this meeting of the Vaccines and Related Biological Products Advisory Committee on

December 12th, 1997.

Pursuant to the authority granted under the committee charter, the director of the FDA Center for Biologics, Evaluation, and Research has appointed the following individuals as temporary voting members: Drs. Broome, DuPont, Karzon, Fleming, Finkelstein, and Snider.

These temporary voting members will participate in the discussion and any votes on the rotavirus vaccine RotaShield™ for the prevention of diarrhea in children sponsored by Wyeth-Lederle vaccines and pediatrics.

Based on the agenda made available, it has been determined that all financial interests in firms regulated by the Center for Biologics, Evaluation, and Research that may be affected by the committee's discussions which have been reported by the participating members, temporary voting members, consultant, and guest speaker as of this date, present no potential for an appearance of a conflict of interest at this meeting with the following notations and disclosures.

Dr. Adaora Adimora reported that in the past she was the principal investigator on an unrelated contract awarded to her employer from a regulated

firm, and in addition, an appearance determination was updated by the agency in April of 1997 for an unrelated grant from NIAID in which she receives part of her salary.

Ms. Rebecca Cole disclosed that she attended an unrelated dinner honoring the developer of the varicella vaccine. She received an honorarium.

Dr. Clements-Mann has been excluded from participation in the discussions on rotavirus.

Dr. Kathryn Edwards: a written appearance determination was approved for an unrelated grant and three unrelated contracts from NIAID, as well as for an unrelated contract from a regulated firm. Dr. Edwards has also disclosed that in May of this year she spoke on an unrelated issue sponsored by a regulated firm and received an honorarium.

Dr. Mary Estes: a waiver was approved for indirectly-related grants. The waiver permits her full participation in today's discussion. In addition, she disclosed that she was an invited speaker for a regulated firm. Also she disclosed that she is working in the rotavirus field and is currently a member of her university's patent team.

Dr. Patricia Ferrieri: the agency approved a waiver amendment in April of '97 for stockholdings.

The holdings remain unchanged. In addition, the agency approved a written appearance determination on October 23rd, 1995, for an unrelated NIAID contract.

Dr. Harry Greenberg has been excluded from participation in the discussion on rotavirus.

Dr. Caroline Hall: an appearance determination amendment was approved for a somewhat-related NIAID contract. In addition, the agency approved an appearance determination in April of '97 for an unrelated NIAID contract.

Of the consultants, Dr. Thomas Fleming, the agency approved an appearance determination on April 4th, 1997, for unrelated NIAID grants.

Dr. Neal Halsey, a consultant, reported that he participated in three different unrelated industry-funded conferences. he received an honorarium plus travel expenses. In addition he reported that he is the co-investigator on an unrelated NIAID grant.

He is also establishing an institution for vaccine safety at Johns Hopkins University. Startup funds have been requested from several vaccine manufacturers. To-date, two manufacturers have provided funding.

In addition, Dr. Halsey reported that he was the investigator on a past NIAID grant in 1985 to 1988

to study rotavirus vaccines, which was awarded to his university.

He is the director of the Division of Disease Control in the Department of International Health. Two faculty members in this division have participated in the efficacy trials under review. Dr. Halsey did not participate or receive any compensation from these studies.

Dr. David Karzon reported that he is professor Emeritus at the Department of Pediatrics, Vanderbilt University. Vanderbilt participated in the vaccine trials with regulated firms. Dr. Karzon did not participate in the trials, nor does he supervise staff working on the trials.

Dr. John Modlin: a waiver for stockholding was approved permitting Dr. Modlin's full participation in the discussions and any vote. In addition, he attended an unrelated vaccine consultant's meeting in October 1996 supported by a regulated firm. He did not receive any remuneration.

In regards to FDA's invited guest speaker Dr. Roger Glass, the agency has determined that his service is essential. He has no reported financial interests which would present a conflict of interest.

The following participants did not have any

financial interests to report on this topic: Drs. Broome, Finkelstein, Meier, DuPont, Maldonado, and Snider.

Screenings were conducted to prevent any appearance, real or apparent, of conflict of interest in the committee discussions today. Copies of all waiver statements and appearance determinations addressed to this announcement are available by written request under the Freedom of Information Act.

In the event that the discussions involve specific products or firms not on the agenda for which FDA's participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

With respect to all other meeting participants we ask in the interest of fairness, that you address any current or previous financial involvement with any firm whose product you wish to comment upon.

CHAIRPERSON FERRIERI: Thank you very much. We'll begin then, with the introduction by Laraine Henchal from FDA.

DR. HENCHAL: Good morning. The vaccine to be presented for the Advisory Committee's

consideration today is RotaShield™. It's a live, oral, tetravalent vaccine for the prevention of rotaviral gastroenteritis. It was submitted by Wyeth-Ayerst Laboratories, also known as Wyeth-Lederle Vaccines and Pediatrics, among other names. It will be referred to from here on as just Wyeth.

The product consists of a Rhesus rotavirus serotype G-3, and three human-Rhesus reassortant viruses which express the major neutralization protein representing human serotypes G-1, G-2, and G-4.

RotaShield™ is to be administered orally using 2.5 ml of a citrate, bicarbonate buffer. The buffer neutralizes the acid contents of the stomach which enables the acid labile virus to pass into the gastrointestinal tract.

The buffer is packaged in a dispette -- in a plastic dispette -- which is also used for administration. The dose to be administered is 4 X 10^5 pfu; that is, 1 X 10^5 pfu of each of the four serotypes. And the recommended schedule is, for infants between six and 30 weeks of age with a 3 weeks minimum between doses, and it would be three doses.

A little bit of the history of this product. In 1987 the original IND for the Rhesus rotavirus serotype 3 was submitted. And then in 1988 the other

INDs for the other three monovalent reassortants were submitted. In 1988 the IND for the tetravalent vaccine was submitted, and in 1997 the PLA and ELA supplement for the tetravalent vaccine were submitted.

There are a total of 25 clinical studies and 15,181 subjects in the U.S. and in seven other countries -- including Brazil, Finland, Israel, Myonmar, Peru, Thailand, and Turkey. There were two other studies conducted in Venezuela under an IND held by the NIH which included another 2,782 subjects.

Of the subjects studied by Wyeth, 957 were neonates -- that is, they were under 14 days of age at the first dose -- and 14,161 were infants. Of the infants, 6,948 received at least one dose of RotaShield™ at the 10^5 pfu dose.

Just a little about the manufacturing and testing. The manufacture is a classical, static, tissue culture method. There is minimal downstream processing. There's just a filtration step and then the vaccine is lyophilized.

The cell substrate is fetal Rhesus lung cell -- oh, I forgot. Because of the minimal downstream processing of this kind of live vaccine, it's important that extensive testing be done to show that the product has been free of adventitious viruses.

In addition to the testing conducted on this fetal Rhesus lung cell line by the originators, Wyeth has conducted extensive and specific testing of the master cell bank for the presence of a number of simian and other agents as shown -- bovine, porcine, and human -- which might possibly be present.

Then they also did testing on the virus seeds for each of the four serotypes, and these have been tested for simian viruses, bovine, murine, porcine, and human viruses as well.

During the nine years of product development prior to submission of the PLA, Wyeth and representatives from CBER have had numerous interactions during which the company received input from various manufacturing, product development, and clinical issues. The review of both the PLA and ELA are ongoing.

I will now present the questions we have for the committee today -- the voting questions.

The first question: Do the data demonstrate the safety of RotaShield™?

The second question: Do the data demonstrate the overall efficacy of RotaShield™ for immunization of the proposed target population?

Third question: Do the data support greater

vaccine efficacy against severe rotavirus gastroenteritis?

Fourth: Do the data demonstrate vaccine efficacy during a child's exposure to a second rotavirus season?

And lastly: Do the data support the co-administration of RotaShield™ with the other routine childhood vaccines given at two, four, and six months of age (such as OPV, DTP, and hemophilus influenza)?

Then we have additional questions that are -- they really aren't questions; they're more discussion points -- that we'd like the committee to comment on; any of these that they believe merit further discussion.

For instance, we would like you to designate if you believe that some of these issues would be advisable for post-marketing studies, for instance. The use of RotaShield™ with other childhood vaccines which are now in current use in that age group -- such as Hepatitis B, the DT acellular Pertussis vaccines and also IPV -- for which data are not yet available with RotaShield™.

The efficacy against rotavirus serotypes that are not prevalent in the U.S. The safety for vaccination for children who are in contact with

compromised hosts. The safety and efficacy when used in infants born prematurely.

And the safety in older children -- and for example, there may be an unvaccinated cohort at time of vaccine release who are older than the recommended 6- to 30-week age period -- and also children who are initiated in the RotaShield™ vaccination series. For instance, say they come in at six months of age, at 24 weeks, and cannot complete the three doses before they are 30 weeks of age.

And then, efficacy when administered to breastfed infants. And that's it.

CHAIRPERSON FERRIERI: Thank you very much. We'll move on then, and Dr. Roger Glass will present on the epidemiology.

DR. GLASS: Thank you very much. I'm delighted to be here and I see this as a very historical event; not only because it's the first rotavirus vaccine to be submitted for licensure, but also because it really is about to mark the 25th anniversary of the discovery of rotavirus by Ruth Bishop in 1973.

Before rotavirus was discovered, diarrheal illness were common but their etiologic source was unknown and they were attributed to the diarrheas of

malnutrition, of weaning -- weaning foods, or physiologic diarrhea.

And it was with the discovery of rotavirus in Norwalk followed by many of the other bacterial pathogens, that we really accept now that there's an infectious etiology for most of these diseases.

This study by Bishop was followed by this photomicroscopy -- electron microscopy -- by Dr. Kapikian in 1974, which was the first discovery of rotavirus here in the United States and has really begun the saga of studies leading to vaccines.

I'd like to cover this morning some of the issues in vaccine development and in the epidemiology of this disease, and why we think it's so important, globally and in the U.S.

Of course, globally as you know, diarrhea is one of the most common causes of death in children. About 25 percent of deaths in children under five are due to diarrhea; that's about three million deaths a year. And once rotavirus was discovered and a diagnostic test became available, it was clear that in developing countries rotavirus was the single, most important cause of diarrheal illness.

When studies were done of hospitalized children, children hospitalized with diarrhea, it was

clear that rotavirus was a democratic disease. That is to say that it infected about a third of children hospitalized for diarrhea in both developed and developing countries alike, and that there was no particular risk group.

It also meant that changes in sanitation or water behavior were unlikely to alter the incidence of disease. When the Institute of Medicine reviewed the disease burden globally, it turned out that every child is infected in the first few years of life and the birth cohort of the world is about 140 -- 130 million children a year. Of these, about one in eight develop severe disease, and the estimate of deaths is now on the order of 600,000 to 800,000 in the published data.

Where do these deaths occur? Well, you can see from this chart, from this map, that most of the deaths are in areas where infant mortality is greatest. About 200,000 deaths in Africa, over 200,000 in India alone, and scattered deaths in the Americas and in other parts of Asia.

And so the Institute of Medicine in 1986 declared that rotavirus vaccine was a priority for new vaccine development in developing countries. Well, they went on and the epidemiologic features here -- we

mentioned most common cause of severe diarrhea in children -- all children are infected in the first three to five years of life. It's a ubiquitous infection of childhood.

Most first infections after three months of age are symptomatic and infections in full term neonates are often asymptomatic. And I'll show you data on the natural history as well.

And finally, because the incidence is similar among children in developed and developing countries, rates will probably not be affected by improvements in water or sanitation.

Well, the first studies here in the United States were these studies by Dr. Brandt and the group at NIH -- Dr. Kapikian and Dr. Chanock -- where they were able to use EM to look at diarrhea hospitalizations in children. And this is a 8-year survey. In black you see rotavirus and it has this distinct, winter seasonable peak, and as a predominant cause of diarrhea hospitalizations in this source -- in this hospital.

Despite these overwhelming data and interesting data the incident of medicine reviewing longitudinal studies in the U.S. decided that this was not really -- there was not enough of a disease burden

in the U.S. to warrant rotavirus vaccine development as a priority for the U.S.

And it was at this time that studies at CDC began to look at the disease burden in the U.S. Our studies which are all published, began at looking at hospitalizations and seeing if -- taking hospitalization from the National Center for Hospital Statistics, hospital discharges which represent a -- and this is a sample of a half-of-one percent of all hospitalizations in the U.S., taking ICD codes for diarrhea of all causes -- because there was no ICD code for rotavirus -- and choosing an ICD code where diarrhea was in the top three causes of hospital discharge.

This eliminates those discharges which occurred in the tenth position, for instance. It might be a nosocomial diarrhea in a patient with another illness. What you can see here is that in the 200,000 hospitalizations each year in the U.S. -- and that's continued; now it's about 160,000 in 1995 -- that there's a marked winter peak which occurs every year.

That peak is primarily in children six months to two years of age, and that peak at least was consistent with what we think of as diarrhea -- just

like we saw in the Brandt study from Children's Hospital.

When we went on to look at this more carefully we found that the peak began or was first seen in the West in the months of November, and was later seen four months later in the Northeast in the months of March and April -- a feature which we had never previously identified to be associated with rotavirus.

We now have laboratory surveillance of 70 laboratories around the United States that report their weekly diarrhea rotavirus detection rates. And what we find is exactly the same; that each year -- and this is for the past year -- the outbreak or the detections began first in November in the Southwest and spread in the same systematic way across the U.S., reaching the Northeast in April and May.

We have no clear understanding of why this seasonal and temporal distribution occurs, but it's clearly a distinct fingerprint of this disease and one which has allowed us to look at other associated -- potentially associated illnesses.

We've taken the difference in hospitalizations in the summer -- the blue line down here, by age -- and subtracted that from

hospitalizations in the winter -- January and February for instance, here in green -- and estimated the rotavirus disease burden as the difference between the winter hospitalizations and the summer hospitalizations as one way to get at this -- to deal with this non-specific data.

And we've come up with estimates and we've estimated two ways. One is that method we call the residual method. The other method is to take the total hospitalizations, the black line on the top here each year, and multiply it by the detection rate by month from that study I showed you by Carl Brandt from D.C. Children's Hospital.

We have a red estimate by Brandt, the blue estimate by the residual method, and what you see is that these two estimates overlie each other almost completely -- a very high correlation -- and the estimated number for this period, 1979 to '92, about 54,000/55,000 hospitalizations for rotavirus a year.

So this has been the estimate that we've worked with and we've played with this in a variety of different ways and I want to show you that later.

Secondly, when we've gone to look at diarrheal deaths we've found that there's a similar peak in diarrheal deaths. There were about 1200 per

year in 1970; there are now about 300 per year since 1985. And you see this distinct winter peak of diarrheal deaths, primarily in children four to 23 months of age.

And that we feel, might have been due to rotavirus in the past. It had the same temporal and geographic migration across the U.S., and that's interestingly come down over time -- really, up until 1985. We don't know why it's come down but it's been associated with a continuation of hospitalization rates, so we think that this may be due to improved treatments or to better access to care.

Nonetheless, if you look at the curve down here, we still have a small, residual peak of diarrheal deaths in the winter seasons, about 20 to 40 deaths a year, which we think is potentially attributable to rotavirus.

So when we began these studies we had never had a documented rotavirus death in the United States and it was never considered a severe disease. From these early data you can see that we probably did have considerable numbers of diarrheal deaths from rotavirus -- 125 to 150 per year -- and these have diminished markedly until 1985.

Based on these initial estimates we could go

back and reconsider that recommendation at the Institute of Medicine and say that in fact, the disease burden of rotavirus in the United States is significant. Most children will have an episode in their first two or three years of life.

About one in seven children will visit a physician or an outpatient clinic. Now we say about 50,000 -- about 1 in 72, 1 in 75 children will be hospitalized in their first few years of life. And the costs are considerable -- 20 to 40 deaths per year.

So it's based on this that we feel that working towards a rotavirus vaccine would have a major impact on health and hospitalizations. There are a number of potential problems with this data.

One is we could ask, is the sampling representative since we're using a half-of-one percent sample that's well taken by the National Center for Health Statistics? Before there were no codes for rotavirus, but since 1993 codes for rotavirus that are specific, have been introduced.

Does the priority position -- whether we've chosen the third position, alter or change, bias our results? Clearly, if we used all positions we would get nosocomial diarrhea which we know for rotavirus,

is important. By choosing only the first we would lose about 20 percent of hospitalizations where the first cause of hospitalization might be dehydration or electrolyte imbalance.

And finally, could our estimation methods be refined? Our efforts in the past two years have really been to improve the estimates that we're making and to put in place a system to monitor the impact of vaccine once a vaccine strategy were implemented.

I'm going to review briefly a number of studies dealing with National Hospital Discharge Data using specific codes for rotavirus done by Umich Parishar in our group, two state surveys from Connecticut and New York, which use 100 percent sample of all hospitalizations.

In New York State for instance, that gives us ten times more data then we have from our national sample by using that 100 percent sample from a big state.

Another study of HMOs which we feel had the lowest rates of hospitalization and which would be the most severe test of how a vaccine might be used and what the disease burden of rotavirus might be.

So those will be the three studies. This is the first data -- a repeat of the hospital discharge

study in which rotavirus code was introduced in 1993. From 1990 to 1992 there were about 163,000 hospitalizations a year for diarrhea of all causes. And what's interesting is that about 70 percent of these are no specified etiology; 25 percent are attributed to viruses and not specified.

Since 1993 a rotavirus-specific code was introduced and immediately -- and I think to my surprise -- in the first year 13 percent of these diarrhea hospitalizations were coded at rotavirus. It's now about 20 percent and for the 3-year period it was 16 percent, representing an estimated 26,000 hospitalizations for rotavirus that are specifically coded.

Now, we don't expect most of these to be coded, so the fact that we have so many coded, this represents about half the estimate of what we would expect. So at least it gives us more specific data to work with.

Well, what can we use this data for? The first use we had was to look at the age distribution. From our earlier survey we said that rotavirus was a disease from six months to two years of age. Using this diagnosis-specific code, we see that there's considerable rotavirus in the first three or six

months of life here; about 15 percent of the cases occur by six months of age.

But more interestingly, about 60 percent of the disease occurs after the first year of age. This means that if we don't vaccinate until later in the first year of age a child still will have 60 percent of its disease burden in front of it. This is quite different than what we see in developing countries, and it is quite different from what we see in the American Indian Reservation from the studies of Mathu Santosham.

In this setting we would expect the vaccine to have efficacy in the second or perhaps the third year. In a setting where most children are infected in the first year of life we cannot expect vaccine efficacy for a longer duration.

We've gone on to the state of New York, and here you can see that hospitalization pattern looks exactly like that of the nation. There are about 12,000 hospitalizations for diarrhea in this state -- and this is a study by Helen Cicirello. In 1993 the rotavirus code was initiated and about six percent of these cases are now coded as rotavirus, and there's been no appreciable decline in the number of hospitalizations over time.

When we look at the seasonability of disease we can see the same feature that we saw in the rotavirus-specific codes, which is to say that the seasonable distribution is about the same. The winter peak in February or March here is the same for all age groups, suggesting that rotavirus is a disease of importance in the younger ages -- in the children under six months -- as well as children over two years of age.

While the numbers are small it's still a continuing problem. It really confirms what we found from the rotavirus-specific coded data.

We then went to Connecticut -- and this a study by Mark Chung at Yale. He looked at hospitalizations the same way. Here it's by quarter instead of by month, and you can see that there's the same winter peak which we would associate with rotavirus but that the numbers of hospitalizations has come down continuously over the past ten years.

In this period of time, there were no hospitalizations in HMOs in the state of Connecticut. Right now about 40 percent of the hospitalizations are through prepaid group practices or HMOs. And we think that some of this decline may be due to a difference in payment, and that comes out in the data.

Another feature we can find in this study is that of the 1200 cases per year of diarrhea, an estimated 450 that are due to rotavirus, of those 83 that are coded for rotavirus specifically, we actually have duration of hospitalization -- about 3.1 days for hospitalization -- and a cost per case of about $3500 per case if hospitalized.

So now that we have ICD-specific codes for rotavirus, we're in a position to look more carefully and more specifically at outcomes and to use this as another way to monitor impact of vaccination when and if the vaccine is introduced.

Well, the last new study is one from Kaiser Permanente. It's part of the CDC's vaccine safety datalink project in which at four Kaisers on the West Coast -- Kaiser of North California, Southern California, Portland, and Seattle -- these four centers which represent two percent of the birth cohort of the U.S. provide all data on hospitalizations and doctor visits, emergency room visits, to CDC to look for adverse side reactions to other vaccines.

It turns out that in this data set that had never been look at for diarrheal events, diarrhea was the number-one cause of doctor visits.

And what you can also see that was interesting is that there's this peak of hospitalizations for diarrhea in the winter season -- in December/January here in California; in February/March here in Portland, Oregon -- the same geographic distribution that we've seen elsewhere; suggesting that this really is rotavirus.

Another feature is that because these are HMOs and Kaiser, physicians are actively discouraged from using a rotavirus diagnostic. And so the physicians didn't feel that this was a major problem.

When we analyzed this data collected through the VSD project, you can see that the main cause of hospitalizations -- for instance, here in Southern California -- is for that winter disease. And this is what we would expect to be ameliorated or prevented through the use of a vaccine.

So our next study in this and other settings, is to begin to introduce stool samples. What we've estimated now -- a number of estimates from the early study or the Institute of Medicine where 1 in 166 children was hospitalized for rotavirus, and a single study by David Matson where 1 in 36 children in the nation would have been hospitalized for rotavirus.

To our own studies which began -- where we

thought that about 1 in 40/1 in 50 children were hospitalized -- now our rates are up to about 1 in 77. In the State of New York it's 1 in 77 exactly; in the State of Connecticut it's about 1 in 110; and in the HMO data it would be about 1 in 140 children being hospitalized for rotavirus.

How do these compare with other studies? We have three international -- actually four international reviews -- one from Australia that's not here. In the review by Brian in the U.K., about 1 in 40 children in the United Kingdom would be hospitalized for rotavirus; in the Finnish vaccine trial of the placebo arm, about 1 in 50 children; and in the Venezuela trial, about 1 in 33 children.

So our rates of hospitalization for rotavirus in the U.S. are considerable. The risk factor that probably most determines the rates of hospitalization our context may be mode of payment and health insurance -- and we don't think it's related to disease incidence.

Well, what we need clearly, is better stool sampling and rotavirus testing and surveillance, so we have very specific data on the disease burden.

I want to just mention serotypes because those will come out in coverage. In our global

collection of strains in serotyping, serotypes 1, 2, 3, and 4 are clearly and by far, the most important, and in these United States these have been the predominant types since we've been serotyping.

This is interesting because 99 percent, or 98 percent of our population is naturally immune, and despite this high level of natural immunity, we don't have a lot of new serotypes arising. So we don't expect this to change much with vaccination, although we have some reason to be concerned in developing countries.

Natural immunity to rotavirus has been documented also through epidemiologic studies. The incident of rotavirus clearly declines with increasing age -- from zero to three years; where studied, repeat disease is uncommon; and children who have been followed up for neonatal infections -- both by Ruth Bishop and Rajvan in India -- suggest that protection is quite good.

I want to present three slides by a recent study by Velazquez and Guillermo Ruiz Palcios in Mexico which highlight the importance of natural immunity and document in a natural sense, how this live, oral vaccine might work as a vaccine.

In this study in Mexico, a cohort of

children was followed from birth. And here you see the accumulation of first infection: that by two years of age most children had had at least one infection; many children, 70 percent, had had two infections; 40 percent had had three; 20 percent had had four; and ten percent or more had had five.

So rotavirus is a disease which can infect children repeatedly. What is the outcome of this infection? Well, this is what happens with disease and if you just look at the ochre here, severe disease is primarily in children in Mexico from four months to nine months of age, and then severe disease is quite uncommon.

Asymptomatic infection is high in the first three months of life and out here with increasing age, and disease becomes increasingly mild or undefined as you get older. So that severe disease is concentrated early in life, asymptomatic infections are more common in very young age group.

Does this natural infection protect? And this I think, is the most interesting slide because if a child has been infected one time, their protection against severe disease is about 87 percent; against mild disease is less, 73 to 77 percent; and against asymptomatic infection, quite low.

With second infection and third infection protection here is complete against severe disease, and higher against milder disease. So that with each subsequent infection your risk of disease goes down. And that's part of the idea which will be replicated in the vaccine; that it's most protective against severe disease.

Finally, when we look at the serotypes, the G types of the first and the second infection, there's actually some demonstration of protection which is serotype-specific. And this has been demonstrated in other studies before but there's both a heterologous and a homotypic protection from rotavirus infection.

Well, the prime target of rotavirus disease besides the U.S. is in developing countries. And the differences in the epidemiology have some clear impact on how we think about vaccines in our own country. The epidemiology is different in a number of ways.

In the U.S. and industrialized countries, this is a winter disease, which means that a child born in March has to wait a full year to get their next infection. That is to say they will be older, and by one year of age about half or 60 percent of them will have an infection.

In developing countries a child born in

March can be infected any day of the year, so that by one year of age 90 percent will be infected. So in our American Indian population we can't expect in this setting, the vaccine to be very efficacious in the second year of life.

Also it means that when we immunize these children we will have to immunize them at a very early age for the vaccine to cover the disease that's important. In the U.S. we usually find a single strain of one of those four strains with common serotypes, and in developing countries we have a completely different situation which I'll show you.

We don't know much about the basic epidemiology of this disease. We don't know the reservoir -- we believe it's humans; we don't know the mode of spread -- we think that it might be airborne droplets or contact but we really don't know; we don't know where the disease goes in the summer. So there are many basic questions that we may not answer and in fact, introduction of a vaccine may be one way to address some of these difficult questions.

I just want to show you the impact of the difference in age of first infection. Here in the United States, 60 percent getting their infection in the first year of life, and in a developing country

about 90 percent.

So that if we immunize in an Indian setting in the U.S. we may miss a substantial number of infections which will have occurred before three doses of the vaccine are fully administered.

And the idea therefore has grown and nearly 1,000 children have received a neonatal immunization, and that may be the way to go for developing countries -- just like it's been the way to go with polio.

How about reassortment of vaccine strains? We know that this virus can reassort. Well it's been interesting that in most developed countries we rarely see more than one rotavirus infection in a single stool sample; whereas in studies in Brazil and in India, 10 to 30 percent of those children will have two serotypes at the same time.

We know from lots of studies that co-infection of cells can lead to reassortment. Here we have children whose intestinal epithelial cells are being co-infected. And what happens? We've been doing studies in India for a long time now and we find that while serotypes 1 to 4 are common in the world, in India serotype 1 is hardly present, serotype 9 -- which was only found once by Fred Clark in the United States -- is the most common serotypes, and there are

a whole variety of other serotypes present.

In fact, in our studies now in Bangladesh we have multi-gene reassortants for all the G-9 strains that we have. So that reassortment can occur, particularly in a setting where you have lots of different viruses co-circulating.

We haven't found this here but it clearly is something that we can expect and should not be remiss of.

Oral therapy: are there other strategies to address rotavirus diarrhea? Oral therapy is used worldwide and has probably been responsible for the oral therapy and IV therapy for the decline in mortality that's been seen from this disease. At the same time, we still have disease despite an oral therapy program in this country and so vaccine would represent primary prevention.

What are the other risk groups for rotavirus in the U.S.? There are some groups which may have increased exposure to virus. Children in daycare centers have been identified repeatedly; nosocomial infections in hospital wards; and in adults, caretakers and parents of these children, travelers to developing countries, and here, groups with impaired immune response -- immunodeficiency disease.

How big are these groups? I think in children in daycare centers what we're seeing is really the concordance of disease at the same time. All these children would have been infected in the same winter but because they're in a daycare center they're easy to identify. So while modes of transmission might be slightly different, this group is really a group in a community and is not particularly at great risk.

Hospital wards -- we find significant rotavirus as a cause of nosocomial disease. This has not been accounted for in the disease burden estimates that I presented earlier, and there could be a significant benefit from a vaccination program.

And caretakers and parents are particularly interesting because this probably represents an alternative mode of transmission which is important. A higher dose for which immunity -- and these caretakers should be immunize -- cannot resist.

Well, where do we go from here? I put this slide up because I see Al Kapikian here at the bottom of the totem pole, and 24 years ago Al made his discoveries of this bar in the U.S. and has really led the fight to have a vaccine, and all the rest of us have been piling on the top of this effort.

Through this effort we've learned that rotavirus is the most common cause and most important cause of severe disease in children, and a vaccine would potentially stop the great burden of hospitalizations and costs associated with this, as well as the illness.

We've learned that the vaccine are likely to behave like natural infection, protecting greater against severe disease. We've learned that endemic disease -- that this is an endemic disease that all children are at risk, and it's hard really to identify major risk groups that would preferentially want to receive the vaccine.

The risk groups of premature children who are immunocompromised are relatively small and we have very previous little data on how natural disease affects them.

Alternative treatments are unlikely to change the hospital rates that we've seen, leading to the idea that vaccines would potentially be more important. Basic epidemiology -- what's the reservoir, what are the modes of transmission? We really don't have adequate data on that and we may not have it even after the vaccine is introduced.

And clearly, the usefulness of the vaccine

will be not only in the United States but in developing countries where this is a major killer of children.

Ultimately, we would like to use the surveillance we've established to document a change in the cutting off with the peaks of diarrhea hospitalizations in this country, within one or two years of the time the vaccine is introduced.

Thank you very much for your attention.

CHAIRPERSON FERRIERI: We have a minute or so for questions from the panel. Dr. Hall.

DR. HALL: Roger, thank you very much; very nice presentation. Do you include the parent and caretakers of these children in one of your target groups because they have symptomatic infection or just because they may be a mode of transmission? And do you have an estimate of how often they will have symptomatic infection or just silent infection?

DR. GLASS: I don't have any estimate on the disease burden of rotavirus in adults. And this could be a very interesting part of this equation which we haven't addressed. We've had outbreaks of rotavirus in nursing homes, which we never expected and I think that shook me two years ago to think that this might be potentially a vaccine for the elderly.

We have rotavirus in travelers to developing countries. All of those travelers are naturally immune so that their immunity is not enough to protect them from disease. Perhaps a problem of a high inoculum of water borne or food borne rotavirus that overwhelms immunity.

In our disease burden estimates we don't have any idea of the number of caretakers or parents who actually get rotavirus disease. And I think it's only been looked at in small studies; we've never looked on a broader.

When we look at hospitalizations -- we're just starting to look now at seasonality of hospitalizations in adults, and I think within six months I'll have data on whether there's an excess in any group of winter hospitalizations with this migratory pattern that could be associated with rotavirus.

DR. HALL: May i just follow that up? Is the immunize response in a subsequent in a second or third infection, somewhat patterned by the serotype that they got of the first infection?

DR. GLASS: Yes. The first infection is usually serotype-specific and is most specific. With subsequent infections it's broader. One of the

interesting features in the Mexican study is that the first infection protects against severe, subsequent disease, which means that there must be protection against the other serotypes as well.

It's not specifically stated, but that's one of the implications. Otherwise, you would expect the second or the third infection also to have the possibility of being severe.

CHAIRPERSON FERRIERI: Dr. DuPont.

DR. DuPONT: Roger, I want to ask about severe disease, which is what we're really aiming the vaccine to prevent, and relationship with age and with serotype of rotavirus.

It's my understanding that most of the severe disease is in young infants, and I'm wondering if the group beyond the age of two commonly develops severe disease or whether this is primarily a problem under the age of two? And then I wonder if there's a relationship between serotype and severe disease?

DR. GLASS: On the first issue of whether there is severe disease over the age of two, the first inkling that we have is from the hospital surveillance study in which the ICD codes have been specified as rotavirus. And in that study, 25 percent of the severe -- of the total of severe disease is in

children over two years of age.

So I would say there is severe disease in children over two, but the incidence is less than in the younger children.

DR. DuPONT: How about over the 30 month period of time? The more than 30 months? Will there be severe disease beyond 30 months?

DR. GLASS: Beyond 30 months? I'd have to go back and look at the slide. For that slide also, we're trying to go back and confirm now that those patients that were coded as rotavirus, in fact, have a rotavirus diagnostic code done, a diagnostic test done.

In many cases we know that to be the case, but in some cases it may just be winter diarrhea that's coded. So we're trying to go back and specify that and go back to hospital-based studies which have been done to look at the full age spectrum and confirm the results that we find from national data.

DR. DuPONT: Okay, and serotype?

DR. GLASS: And the serotype -- really, we have precious little information on serotype and disease severity. We've looked at a study in Bangladesh and did not find much difference in severities with serotype.

We really haven't looked here carefully at serotype. I think the severe disease has occurred with all serotypes but we don't know whether one serotype would be -- have greater illness or not.

CHAIRPERSON FERRIERI: We have time for two quick questions. Dr. Karzon and then Dr. Fleming.

DR. KARZON: The use of the ICD code has been very productive and a great deal of interesting information, pertinent information has been gathered. What I'd like to know is the basis for the use of ICD code.

What does a physician have to have to check that column? Is there laboratory backing for it, or does this vary from site to site?

DR. GLASS: When we started these we didn't know what to look for, David, because most of these, 70 percent are coded as diarrhea, no specific etiology.

And what we found was a very specific -- we started knowing the rotavirus from the studies of Kapikian and Brandt would represent about a third of hospitalizations, so it was a predominant cause, it was in young children, and it had a winter seasonality.

And those three features led us through the

ICD code to identify all the ICD codes for diarrhea of infectious or non-infectious origin, and put them together and came up with our early estimate. It's only now since '93 that we have an ICD code that's specific for rotavirus, that we can work with and try to be more specific.

What a physician has to -- a physician now can code rotavirus which he could not have coded three years ago. Also, this will help us in thinking about mortality because a physician before could never code a diarrheal death as rotavirus.

I would say that there have been no rotavirus deaths in the United States that are reported or coded because there's no code available. Since 1993 we now have that possibility to begin to survey deaths.

CHAIRPERSON FERRIERI: Dr. Fleming.

DR. FLEMING: A comment and a question -- just a comment relative to the earlier question. In fact, I thought your statistics from the HMO had suggested that up to 60 percent of the hospitalizations actually occurred after age one.

And the question is, my sense from your epidemiologic survey is at least much of the focus of the clinical impact here is in hospitalization where

rates maybe are on the order of 1 to 50, 1 to 100, and you're estimating the economic burden of that would be average $3500, which would be then by age five, per individual, $35. Am I interpreting your --

DR. GLASS: That's right. I want to say one other thing. With the HMO data it was interesting to me -- and we're involved now in a study in Kaiser of Southern California -- there, 80 percent of their disease is in the winter season when rotaviruses should represent, you know, 70 percent of those hospitalizations.

So the total impact in an HMO for rotavirus could be significantly greater than what we would estimate using our other estimators. It could be significantly greater.

CHAIRPERSON FERRIERI: Thank you, Dr. Glass. We'll move on to the sponsor's presentation, and if we stay on schedule then there will be room after that for some more questions, and something that might have occurred to you to ask Dr. Glass can also emerge during that time.

Dr. Peter Paradiso will lead off for the sponsor. Good morning, Peter.

DR. PARADISO: Good morning, Pat. As was just said, my name is Peter Paradiso. I'm vice

president for Scientific Affairs and Research Strategy at Wyeth-Lederle Vaccines and Pediatrics -- which we heard this morning has now been shortened to Wyeth, thanks to Laraine Henchal and we appreciate that.

Over the next several hours we're going to review the clinical data that constitutes the basis for our license application for RotaShield™ in infants. As mentioned earlier, there's going to be a lot of data presented at this presentation. What we would like to suggest is that substantive questions be held until the end for the discussion period, but obviously we'd be happy to answer questions for clarity throughout the course of the presentations.

Roger has reviewed the epidemiology of rotavirus gastroenteritis in detail so I'll only briefly reiterate, the burden of disease associated with this virus and the reason for our work in developing a vaccine to protect infants from this disease.

And I should say that, as you can tell from that fine presentation that Roger made, that if there was a totem pole next to the one that Al Kapikian is on the bottom out there, would be one with Roger at the bottom as the epidemiology totem pole for defining this disease burden in the U.S. and around the world.

Rotavirus is the major cause for gastroenteritis in U.S. infants, and in fact, in infants around the world. It is estimated that 75 percent of children are infected by the age of five years, and the virus is estimated to be responsible for between 30 and 50 percent of all hospitalizations for gastroenteritis in U.S. children, with a significant peak disease in the winter season where it accounts for between 70 and 90 percent of severe disease.

Globally, rotavirus is a significant cause of mortality in young children. While not the subject of this morning's meeting or this application, our hope is that our rotavirus vaccine will ultimately have a significant impact on rotavirus disease worldwide.

RotaShield™ is a live, oral vaccine containing four virus strains. The so-called Jennerian approach was used to develop this vaccine taking advantage of the ability of the Rhesus rotavirus to infect humans without causing gastroenteritis.

The vaccine contains four virus strains shown here, including the parent RRV strain, which cross-reacts with the human serotype 3 virus, and

three reassortant viruses which contains the parental backbone from RRV but substituting the human VP7 proteins from serotypes 1, 2, and 4.

The vaccine therefore induces an immune response to all four human serotypes. RotaShield™ will be given to infants at two, four, and six months of age for the prevention of gastroenteritis due to rotavirus.

It is worthwhile to take a second to review the history of the development of this vaccine over the last 25 years. The virus was first discovered in Ruth Bishop's lab in 1973, and within ten years the first live, attenuated vaccines were clinically tested. Major scientific milestones resulted from the work in Al Kapikian's lab in the NIH in the mid-1980s.

These were the identification of the four, disease-causing, human serotypes, the demonstration that human/animal reassortants could be derived, followed by the first clinical trials of these prototypes.

It is important to note, as has been noted already, that Dr. Kapikian is not only the originator of the vaccine which we are discussing today, but is universally recognized as the champion of rotavirus vaccines. And Dr. Kapikian is in the audience today.

Several of his co-workers, including Dr. Greenberg and Mathuram are also here today.

Wyeth-Ayerst became involved in this program through a CRADA with the NIH in 1988 around the time that the first reassortant trials were being reported -- the first by Neal Halsey and co-workers. Neal is also here today; there's a recurrent theme.

These trials were followed by tests of the tetravalent vaccine and in 1996 Dr. Margaret Rennels reported the results of a multicenter, U.S. efficacy trial with the formulation we will discuss today.

This year we filed our license application for RotaShield™ and very recently, the data from efficacy trials in American Indians, Finland, and Venezuela have been published. And just for completion, the American Indian trial was done by Dr. Mathuram Santosham, and he is also here today in the audience.

As the history slide shows, the testing of RotaShield™ and its ancestors progressed from the testing of the monovalent parent vaccine at various doses, to tests of the reassortants as the need for multiple serotypes was recognized. The final formulation, the vaccine for which is being presented today, contains the four viruses and 10^5 plaque-

forming units of each type.

The experience that we will be reporting today with this formulation, includes immunization of 6,948 infants given nearly 20,000 doses of vaccine, including three placebo-controlled efficacy trials. In addition, results using the same vaccine in Venezuela have just been reported in The New England Journal of Medicine.

These data in over 1,000 Venezuela infants add to our confidence in the safety and efficacy of this vaccine, but are not part of the current application and will be discussed only briefly in the conclusion.

The clinical presentation today will be given in large part by Dr. Joe Camardo, director clinical research of Wyeth-Ayerst. Dr. Camardo, along with Dr. Ed Zito -- who is sitting here and is responsible for the slides that you're seeing today -- has been responsible for this clinical program since its inception.

The program will include a clinical overview, immunogenicity data, efficacy data -- including a report on the U.S. multicenter study that will be given by Dr. Rennels -- and then finishing with the safety data analysis in the end.

I will be back to conclude and then we are of course, all available to answer any questions. So I would like to ask Dr. Camardo to come up. Thank you.

CHAIRPERSON FERRIERI: Thank you, Dr. Paradiso. Just a reminder to all the speakers to please conform to the time allotted to there will be time for questions.

DR. CAMARDO: My problem is usually finishing early.

CHAIRPERSON FERRIERI: Oh, we'd love that. That's wonderful.

DR. CAMARDO: Peter, thank you very much. It's really a privilege for me to summarize for you, a large body of safety, efficacy, and immunogenicity data that represents the work of many people over many years. And this work is the basis for the product license application for RotaShield™.

I'd like to give you an idea of how long this program has gone on, and we wanted to have the first vaccinated infant actually be at the committee meeting but unfortunately the person is now a sophomore at Stanford and has final exams. I know I said I wouldn't deviate from the script, but it's just to slow me down a little.

(Laughter.)

This slide is a computer-generated model of rotavirus. As all of you know, this is a triple-layered particle surrounding the double-stranded RNA and the two outer layers are shown here. Two proteins of the outer capsid, the VP4 and the VP7, and one protein of the inner capsid, the VP6, are highly immunogenic.

The VP6 is group-specific and the group A rotavirus is that in fact, humans are classified further into P serotypes based on the VP7 -- I'm sorry, based on the VP4, and the G serotypes based on the VP7 antigenic specificity.

Four of the G serotypes in group A cause the majority of disease in humans, and the VP7 antigen specific for these four serotypes are included in RotaShield™.

The features of rotavirus infection that are relevant to vaccination are the following. First, we need to remember that rotavirus is a mucosal disease. Infection of the cells of the villus epithelium of the small intestine causes a characteristic watery diarrhea.

Second, similar to many of the enteric infections, natural immunity is neither lifelong nor

complete and reinfection does occur. However, as Roger showed you very nicely in the paper from Dr. Velazquez and his colleagues, repeated infection has a cumulative benefit against subsequent disease, and even a single episode of rotavirus diarrhea has been shown to reduce the severity of a later episode to mild or even asymptomatic.

It's very important that we keep these facts in mind when we discuss the efficacy of the vaccine, how the efficacy data were analyzed, and what this means clinically for the infants.

There are three properties of the immune response that are critical to our understanding of RotaShield™. First, mucosal antibody does play a role in the prevention and amelioration of illness. Second, serotype-specific protection, that is homotypic immunity, is thought to be important for protection against the first infection.

And third, although serotype-specific antibody is detected in the serum after rotavirus infection, no specific serum antibody or antibody titer has been shown to confer protection against infection.

Absent this, the only approach is to characterize the repertoire of known immune responses

and try to include these in the responses to the vaccine. Therefore, the objective of the research was a rotavirus vaccine that would be likely to induce the complex immune response analogous to natural infection, including mucosal and serum antibody against the common circulating Group A rotaviruses; thus, the use of a live virus.

The vaccine was made by taking advantage of two properties of rotavirus. First, host range restriction which limits the pathogenicity to the usual hosts, and second, the segmented genome which permits reassortment of the genetic material.

The Rhesus rotavirus type 3 which shares 96 percent homology with the VP7 of the human type 3, does cause illness in Rhesus monkeys, and it is immunogenic in humans but it doesn't cause illness in humans. This virus was used by Dr. Kapikian as the substrate to endow RotaShield™ with proteins specific for the other human serotypes 1, 2, and 4.

This shows the two immunogenic, outer capsid antigens, the VP4 and the VP7. To create the four individual vaccine viruses, cells were co-infected with Rhesus type 3, and serum types 1, 2, or 4.

Progeny various were then selected for reassortants that expressed ten of the original genes

-- including the gene for VP4 in the blue -- and one gene from the human virus, the VP7 in the red. Thus the progeny viruses retain the restrictive pathogenicity of the parent but induce serotype-specific immunity to human type 1.

This co-infection and selection process was repeated to produce the reassortants 2 and 4. And as you've already been told, the original serotype 3 is included in the vaccine since VP7 antibodies to the string cross-react with the human type 3.

In two of the studies you will hear about today, a monovalent vaccine including only the serotype 1 reassortant, was tested along with the tetravalent vaccine.

The clinical development program was designed to accomplish the following major objectives. First, to demonstrate in controlled clinical trials that RotaShield™ protects infants against rotavirus gastroenteritis. Second, to demonstrate safety -- most importantly, the absence of rotavirus disease caused by the vaccine itself.

Third, to characterize the immunogenicity of the vaccine. Fourth, to show that RotaShield™ can be administered along with other vaccines for infants, and in infants who are breastfeeding. And fifth, to

use the immunogenicity data to demonstrate that large-scale lots of RotaShield™ can be manufactured to specifications defined by the efficacy trials.

The development program comprises 27 clinical trials of the different generations of this vaccine in more than 17,000 infants, neonate, and adults. Two of these studies were performed by the National Institutes of Health under a separate IND.

These 27 studies were done in the United States, Finland, Peru, Israel, Brazil, Myonmar, Thailand, Turkey, and Venezuela; in different populations, in different conditions, and in different epidemic years.

These studies included doses ranging from 10^3 plaque-forming units of the monovalents, up to 4 X 10^6 plaque-forming units of the tetravalents. But during the presentation, unless specifically stated, RotaShield™ means the tetravalent vaccine at 4 X 10^5, which is the dose for which the application was submitted.

Of the 25 studies of the different doses and formulations sponsored by Wyeth, eight clinical studies comprised the RotaShield™ database pertinent to our discussion today. There are five placebo-controlled studies and three of these are randomized,

placebo-controlled, large-scale studies.

There are three non-placebo-controlled studied as well, a total of 6,948 infants received at least one dose of RotaShield™, and 6,229 received all three recommended doses. And 2,222 infants received placebo.

The three efficacy studies are the U.S. multicenter study of RotaShield™ placebo in the monovalent vaccine in which approximately 1,300 infants participated. The American Indian study which has a similar design and included just under 1200 infants, and the Finnish study which includes only RotaShield™ and placebo in about 2400 infants.

There are additional studies including a large-scale study of safety and immunogenicity, a study of vaccine shedding, a placebo-controlled study to rule out interference of RotaShield™ with DTP-Hib, and a study to demonstrate the consistent immunogenicity and safety of five large-scale manufacturing lots.

There's one recently completed study for which data are not yet available. This is the study in Finland to demonstrate that RotaShield™ does not interfere with Hepatitis B vaccine and IPV.

I plan to spend only a few minutes

discussing RotaShield™ immunogenicity. There is no established, protective antibody titer for rotavirus, therefore the clinical studies including measurement of several of the known responses to rotavirus infection that are also induced by live virus vaccination.

These are the group-specific, secretory antibody component IgA and serotype-specific, neutralizing IgG to the original vaccine strain, the S3, and the four human serotypes.

Our own analyses in these trials to identify a correlate of protection suggests that efficacy is related to the titer of IgA, but we really can't consider this result definitive, so I want to focus instead on how we characterize the immune response in terms of each of the separate responses through the components of the vaccine.

In these studies serum was collected at baseline and one month post-dose 3. Serum IgA was measured by ELISA -- and this is mostly directed against the VP6. Neutralization assays included the plaque reduction assay, the fluorescent focus assay, and a neutralizing ELISA. The latter two of these are significantly more convenient for large-scale trials but they were correlated with the plaque reduction

assay.

The target for neutralization was either the parent vaccine strain itself, the S3, or one of the four human strains from which the reassorts were derived, not the reassorts themselves. The results are expressed as a percent seroconversion defined as a four-fold increase in titer from baseline to post-dose 3 and as geometric mean titers, and no correction for maternal antibody was made in these calculations.

The immunology results from all of our trials are really pretty much identical, so I want to really show you representative data from the U.S. multicenter study because these data were used to define immunogenicity specifications for five lots of vaccine tested in the consistency lot study -- one large study in which the infants were randomized to the different lots. And I will show you that data as well.

Seroconversion post-dose 3 shown here. For all six assays -- the IgA neutralizing antibodies to the parent virus and to the four human serotypes -- seroconversion is significantly higher in the active, the RotaShield™ versus the placebo group for each of the assays. And in fact, seroconversion is greater than 90 percent to any one of these tests.

Based on these data and the proven efficacy in the study, the specifications for the manufacturing lots required that seroconversion rates for all six assays, each one should fall within the 99 percent confidence limits of the rates for this study.

All five consistency lots met this requirement. This row shows the combined results of the five lots in 1,186 infants, which as you can see, match very well the seroconversion rates from the U.S. study.

The geometric mean titers from the U.S. multicenter study are also significantly higher in the active versus the placebo group for IgA the parent and all the human serotypes that were tested. Based on these results the specifications required that the geometric mean titer for each of these assays also fall within the 99 percent confidence limits of the titers from the infants in the multicenter study.

And as you can see, all five lots met this criteria for each antibody titer, and this row shows that the levels from the consistency trial, match the geometric mean titers from the multicenter trial.

Now, the immunogenicity component of the program therefore, demonstrates neutralizing antibody responses to the parent virus and the four human

serotypes represented in RotaShield™ as well as a group-specific serum IgA response. These are the anticipated results based on what is known about the immune response to wild rotavirus infection.

In terms of seroconversion and antibody titer to each of the components of the vaccine, the immunogenicity of five large-scale lots met specifications set from the serologic results of the efficacy studies and matched the immunogenicity of the vaccine used in the efficacy trials.

No single correlate of immune protection was identified. The data aren't definitive but do suggest that the IgA response is most likely to correlate with protection. This is reasonable considering what we know about rotavirus and the importance of mucosal-based antibody for prevention of mucosal disease.

I want to turn now to the efficacy program to review the clinical trial designs, the endpoints, the surveillance methods, and the analyses. These vary only slightly from one trial to another so I want to present them for all the studies and we'll cite the exceptions when we review the additional studies individually.

All three studies were randomized, blinded, and placebo-controlled. The definitions of the

endpoints were as follows.

Diarrhea was defined as three stools, looser than normal, than in 24-hour period. The parents were asked to record the loose stool count. The incidence of diarrhea per the definition, was derived from the stool count record.

Vomiting was defined as the forceful expulsion of gastric contents. This is obvious, but in a baby you do have to ask the parents to distinguish real vomiting from spitting up a little bit of milk.

Gastroenteritis is an episode of diarrhea or vomiting, also referred to as GE. And the case definition of rotavirus gastroenteritis, or RVGE, was gastroenteritis, and a rotavirus antigen positive in a stool collected during or within one week of the GE episode.

Stools were analyzed at a central laboratory and the results were not revealed to anybody until after the study was unblinded.

Infant eligibility is as follows: boys or girls between six weeks and 22 weeks old at the time of the first dose. We were of course, not inflexible and rigid about this criteria and you will see that infants a week or two older or younger were allowed in

the protocols.

Infants had to be in good health and live in a household with a telephone. This last criterion did not apply in the American Indian study. Infants were excluded for recent illness, including diarrhea or vomiting within three days of the dose. Infants were also excluded if an immediate family member was immunocompromised or if a family member had diarrhea or vomiting within the previous three days.

Premature infants who were otherwise healthy at the time of the first dose were not excluded and a small number were enrolled in the various studies. Surveillance for gastroenteritis of any cause began with the first dose and continued until the end of the rotavirus season, with the most intense surveillance during the immediate post-dose period and during the seasonal rotavirus epidemic.

The post-dose period comprised the day of vaccination through day-5, post-vaccination. An interdose period began with day-6 and continued till the next dose. This was repeated for doses 2 and 3.

After dose 3, the interdose period continued until the efficacy surveillance period began. This period of efficacy surveillance began two weeks after the last dosing and continued until the end of the

seasonal epidemic.

For infants in the U.S. studies the 3-dose series was completed before the epidemic began. In Finland as you will see, the vaccine was administered during the first seasonable epidemic up to the start of the second season. Finally, in the United States the vaccination scheduled for RotaShield™ coincided with the schedule for DTP-Hib, and at least two doses of oral polio vaccine at the time the study was done.

In Finland, one or two doses of DTP were given with RotaShield™. In the efficacy studies, the co-administration of these vaccines at the same visit was permitted but not required by the protocol.

For active surveillance during the rotavirus epidemics parents were contacted by the study site personnel once per week during the season. If an episode of gastroenteritis occurred, daily phone calls were made to assure appropriate collection of stool samples and completion of a gastroenteritis record until the episode resolved.

Parents were called biweekly outside of the epidemic season. Passive surveillance consisted of monitoring the emergency room and the pediatric clinics for GE episodes and identifying the charts of study infants to assure stool sample collection for

any clinic visits for gastroenteritis.

For the U.S. multicenter study and the American Indian study the primary endpoint was rotavirus gastroenteritis of any severity. The secondary endpoint was severe rotavirus and gastroenteritis.

For the Finland study this was reversed. The primary endpoint was severe rotavirus gastroenteritis, and the second endpoint was gastroenteritis caused by rotavirus of any severity.

At least two analyses of efficacy were performed. The primary per protocol analysis included infants who satisfied the protocol criteria, received the first dose within the acceptable dose windows, had the doses separated by at least three weeks, and received all three doses. The efficacy period began two weeks after the last dose.

Stool samples from infants without a matching clinical episode that met the definition of gastroenteritis were not included in the results. The decision to exclude an infant from the primary analysis was made according to the rules of the protocol before the blind was broken, and only one episode per infant was counted.

An intent-to-treat analysis included any

infant randomized to receive the vaccine, regardless of whether the series was completed, with case accrual from the date randomized. And all positive cases counted, with or without a matching clinical episode, in or out of the efficacy period. I'm going to present only the per protocol analysis.

The rates of rotavirus gastroenteritis were prepared using Fisher's exact test, and the P-value was adjusted for the 3-way comparison in the two studies with both the tetravalent and the S-1 vaccine. But I'm presenting the important information which is the efficacy results, and these are all going to be reported with 95 percent confidence intervals.

As Roger told you, severity is an important component of rotavirus gastroenteritis, so the severity of the cases was analyzed and we used a 20 point scoring system. We all know that this kind of approach has limitations but as you will see, this is a logical, intuitive system, and it captures data that allows us to evaluate not just a single number, but all the weight of the evidence describing the effect of vaccination on severe disease.

And also how the severity of rotavirus illness is reduced in infants in whom it is not completely prevented. As you will see, the strength

of these results is that all of these analyses are consistent.

The scoring system supports the comparison of the group mean scores. The individual parameters of the score, and the number of cases higher than a specific cutoff score. All cases of gastroenteritis, whether or not caused by rotavirus, were assessed by the parents based on instructions from the study staff to determine the severity of the illness.

This was performed blinded. Neither parents nor the study staff knew the treatment assignment, nor did they know whether the case was caused by rotavirus or something else. Parents were asked to note the duration of symptoms, the number of episodes per day, as well as the temperature, the use of oral rehydration, and the need for medical intervention until the episode was resolved.

The estimate of the extent of dehydration required assessment by a physician. The record was converted to a score after the database was closed, before the blind was broken. The cutoff scores were assigned to denote cases of severe disease. In the United States the cutoff scores were greater than eight and greater than 14, and the latter denotes the most severe cases.

In Finland in which a different scoring system was used, the cutoff score for severe disease was greater than ten. The number of infants in each group with a score above the cutoff level could be analyzed for the RotaShield™ and placebo groups, and the efficacy at each specific score could also be evaluated.

The scoring systems for the U.S. and Finland trials are shown here, and I will not go through this in great detail. You should note however, that the categories, duration, and number of episodes of diarrhea and vomiting, fever, the need for medical care, dehydration, are the same but there are differences in the points assigned for the different levels of illness.

For example, three days of diarrhea scores two points in the U.S. system but only one point in the Finnish system. Three episodes of vomiting scores three points in the U.S. system but only two points in the Finnish system. Generally speaking, in Finland only hospitalization qualifies as medical intervention, and this receives only two points.

Therefore, an episode of the same intensity and duration in Finland would receive a lower score in the Finnish versus the U.S. trials, and this is shown

on the next slide. And this is also intended to give you a better impression of what the score means in terms of risk of illness to the infant.

This is an infant who had diarrhea for three days -- the scores are on the left and the right -- with greater than five stools per day on at least one day, a maximum temperature of 38.4 degrees, three days of vomiting with more than two episodes on one day. The infant was two percent dehydrated and required oral rehydration. The score in the U.S. was 15; the score in Finland is 11. In both cases this meets the definition for a severe case.

What you will see is that RotaShield™ is most effective in preventing severe disease. This is revealed as a reduction in the duration and intensity of illness in the vaccinated infants who have rotavirus GE. The less severe illness leads to less dehydration, less need for medical intervention, and we've shown in one trial -- actually, two trials -- less need for hospitalization in the vaccinated group.

And these effects will become a lot clearer when you actually see the efficacy data. This is the background. Now what we would like to do is present in detail, the results of the major efficacy trials. And first I've asked Dr. Margaret Rennels of the

University of Maryland, to review the safety and efficacy from the U.S. nationwide, multicenter study which was performed at 24 sites located in the cities that will appear on this map, as Peggy comes up to speak.

DR. RENNELS: On behalf of the United States rotavirus efficacy group I'm going to present the safety and efficacy results of the National Multicenter Trial of the Rhesus-Human Reassortant Rotavirus Vaccines given at the dose for which licensure is sought.

This was a prospective, randomized, double-blind, placebo-controlled trial into which 1278 healthy infants between the ages of five and 25 weeks of age were enrolled through 24 centers located throughout the U.S.

Children were equally randomized to receive three doses at approximately two, four, and six months of age orally, during the non-rotavirus season of either placebo, the monovalent serotype 1 Rhesus-human reassortant vaccine, or the tetravalent vaccine -- RotaShield™.

Serotype 1 vaccine was studied at this point because the wild type rotavirus serotype to most commonly circulate in the U.S. is serotype 1, and at

this point it had not been decided which vaccine candidate to further develop.

I will be emphasizing results however, for RotaShield™. Lyophilized vaccine was reconstituted with a small amount of a sodium citrate/sodium bicarbonate buffer because rotavirus is an acid labile virus. And concurrent administration of routine childhood vaccinations was permitted but not required.

Monitoring for vaccine safety began the day of vaccination and continued through five days after each dose of vaccine. Parents took evening axillary temperatures and maintained a diary of symptoms.

The efficacy period began two weeks after the third dose and continued in this trial through one rotavirus season. Parents were phoned every week and reminded to call the study nurse if their child developed vomiting or diarrhea.

When an episode occurred two stools were collected from two different days and tested for the presence of rotavirus antigen by ELISA and positive stools were then typed using serotype-specific monoclonal antibody.

And every episode of gastroenteritis was scored for clinical severity on the 20 point scoring system Dr. Camardo just presented, with greater than

eight and greater than 14 point episodes being arbitrarily termed severe and very severe, respectively.

On these graphs are the percentage of children who received the RotaShield™, the serotype 1 vaccine, or a placebo who experienced fever, vomiting, or diarrhea following dose 1, 2, or 3, over the entire 5-day surveillance period.

The 95 percent confidence interval bars all overlap showing that there were no significant differences in the rate of these three reactions over the surveillance period. Some mild fevers may have gone undetected however, because of the use of axillary temperatures.

The significant differences had a p of .05, and the percent of children with symptoms on individual days post-vaccination is shown in this table. You can see that on a single day following the single dose, more RotaShield™ recipients than placebo recipients had fever with associated decreased activity both occurring on the same day, and runny nose.

More placebo recipients than vaccinees had irritability. Now there were 135 reaction comparisons with no correction for multiple comparisons, so some

of these differences may be due to chance alone.

During the seven days post-vaccination, five vaccinees and one placebo recipient were hospitalized; two RotaShield™ recipients experienced fever with vomiting and diarrhea, and were shedding vaccine virus. A symptomatic vaccinees also shed vaccine virus.

And though there are no differences in the rates of hospitalization among the groups, concern for these two children led to a comparison of hospitalization rates in the entire database, which Dr. Camardo will be reviewing with you later.

Stools were collected from 86 percent of the 1205 episodes of gastroenteritis and vaccine efficacy was determined using the proportion of children with rotavirus disease. Only one child, a placebo recipient, had two episodes.

During the season of surveillance, two wild type rotavirus strains circulated: serotype 1 and serotype 3. Shown in these columns are the number of subjects experiencing rotavirus diarrhea, all serotypes, and by individual serotypes. The number of evaluable children per placebo group was 385; there were 398 RotaShield™ recipients; and 404 serotype 1 recipients.

Vaccine efficacy for the two vaccines with 95 percent confidence intervals are shown in these columns. Rotashield vaccine efficacy against all serotypes, all severity of disease, was 49 percent; it was 54 percent for the serotype 1 vaccine.

Against serotype 1 disease, RotaShield™ vaccine efficacy was 44 percent; it was 55 percent for the serotype 1 vaccine. And against serotype 3 disease, RotaShield™ vaccine efficacy was 77 percent versus 45 percent for the serotype 1 vaccine. And this is important for years during which serotypes other than 1 circulate.

Vaccine efficacy increased with increasing severity of disease for both vaccines, but moreso for the RotaShield™ vaccine. Again, efficacy against all disease of all severity: 49 percent for RotaShield™; 54 percent for serotype 1.

Against episodes scoring greater than eight points, RotaShield™ vaccine efficacy was 68 percent versus 55 percent for serotype 1. And against the greater than 14 point episodes, RotaShield™ efficacy was 80 percent versus 69 percent for serotype 1.

There was an almost linear increase in the efficacy of RotaShield™ with increasing severity score. And this graph shows you that for every single

severity score there was a reduction in disease rate for the vaccinees compared to the placebo recipients and the percent disease reduction was greatest at the highest severity scores.

We also looked at vaccine efficacy by clinical parameters. You can see that the RotaShield™ vaccination prevented 73 percent of physician's visits for rotavirus gastroenteritis; and that where there were 13 cases of dehydration among the placebo group for rotavirus gastroenteritis, there were no cases of rotavirus dehydration among the RotaShield™ group.

Now, because vaccine efficacy increases with greater severity of the disease, you would expect that a distribution of episodes of rotavirus gastroenteritis by severity scores would show that more cases in the RotaShield™ group fell in the milder cases, and that is indeed, what is seen.

On the *Y* axis is the cumulative percentage of rotavirus positive episodes from zero to 100 percent, plotted by increasing severity score. The orange line are the RotaShield™ episodes and the green line are the episodes among placebo recipients.

The median severity score among the RotaShield™ recipients was less than eight, whereas

it was 11 in the placebo group. And whereas 50 percent of the RotaShield™ recipients had a score of less than eight -- at least there are episodes less than eight -- only 20 percent of the placebo group episodes scored less than eight.

Because rotavirus is the single most common cause of significant diarrhea in young children, we looked at the impact of the RotaShield™ vaccination on gastroenteritis overall throughout the vaccine efficacy surveillance period. And in yellow are the significant differences between the RotaShield™ group and the placebo group.

There were significantly fewer episodes of gastroenteritis of all etiologies among the RotaShield™ recipients compared to the placebo recipients. Significantly fewer RotaShield™ recipients were taken to a physician for gastroenteritis and they were taken significantly fewer times. Three of the children in the RotaShield™ group developed dehydration from gastroenteritis versus 16 in the placebo group -- and remember that 13 of those were due to rotavirus.

So to briefly summarize, we found no significant differences between the vaccinees and controls in the incidence of symptoms over the entire

surveillance period; that there were trends towards higher efficacy of RotaShield™ than serotype 1 vaccine against serotype 3 disease and against severe disease.

And that RotaShield™ vaccine efficacy varied from 49 percent against disease of all severity, to 100 percent against dehydrated rotavirus disease.

And finally I just want to say that this trial represented the work of many, many investigators who are listed here.

CHAIRPERSON FERRIERI: Thank you, Dr. Rennels. We're back to Dr. Camardo.

DR. CAMARDO: Thank you very much, Peggy. I'd like to convince you that a major strength of the clinical program is the reproducible performance of RotaShield™ in different randomized trials in different years and different populations. That's of course, what's going to happen if the vaccine is used in the American infants.

In addition, each trial provided new information to complement the other trials. The three efficacy trials are shown here. You heard about the U.S. Multicenter Trial in detail from Dr. Rennels. The second U.S. trial was performed in American Indian

infants.

The design is similar to the U.S. Multicenter Trial; the same dose and schedule, both the tetravalent and S1 vaccines and placebo are included. However, efficacy was determined in the 1992/93 season rather than the 1991/92 season, and the infants were followed an additional season to about 24 months of age.

The third efficacy trial was performed in Finland from 1993 to 1995. The dose was the same but the schedule was different. Dosing continued through the first season, there were only two groups, and the endpoint was severe rotavirus gastroenteritis.

Let me show you the similar efficacy among these studies then discuss the efficacy from the two trials in more detail, then I want to talk about the overall safety database.

First, all three trials demonstrate efficacy versus placebo in the first rotavirus season after vaccination. The two U.S. studies are nearly identical. The Finland study is somewhat better. I won't read each of these to you but I want you to note the confidence limits on the efficacy estimates from the primary analysis each time I show you efficacy.

Second, in all three trials, efficacy

against severe disease defined as a score greater than 14 in the U.S. and greater than ten in Finland is higher than efficacy against all cases. This is a consistent finding that reflects not just the behavior of the vaccine but the biology of the immune response to wild type infection as well.

Now the American Indian study. This was a randomized, double-blind, placebo-controlled study in 1,185 infants. Dr. Mathu Santosham in the Johns Hopkins Center for American Indian and Native Alaskan Health, worked with us to develop the protocol design and analysis plan, and provided local study staff to assure enrollment, surveillance, and case report form completion.

The Indian Health Service Clinics provided medical care for the infants and participated in surveillance for safety and efficacy. There were seven sites located on reservations of Navajo, Apache, Hopi, and Pima Indians. In this study, the usual telephone surveillance was supplanted by home visits for many of the participant families to assure adequate surveillance.

It's notable that this is a community in which the use of oral rehydration is vigorously promoted; something that I think Johns Hopkins and

Mathu and the center is very proud of, and I think it's very important. The results of this study were published in October in The Journal of Pediatrics.

So 1,051 of 1,185 infants randomized in the trial received three doses of RotaShield™ before the winter rotavirus system and qualified for the primary analysis. Stool samples were available for 66 percent of the cases of GE that occurred during the two years of the study. The missing stool samples were equally divided among the three groups.

The two seasons are analyzed and presented separately and in the first season there were 179 episodes of rotavirus GE. Here are the numbers of cases, the rates, the efficacy and the confidence intervals. On each of these slides I'll present these results in the same format; some of these percentages are rounded off.

Efficacy determined in the primary per protocol analysis was 52 percent for RotaShield™ and 29 percent for the S1 vaccine. The low efficacy of S1 here is explained by the predominance of a serotype 3 strain in this epidemic. This slide shows that in the placebo group, 61 of the 81 cases in the '92/'93 epidemic -- this is the first year of serotype 3.

The efficacy of RotaShield™ against

serotype 3 was 56 percent. Note again the confidence intervals versus the efficacy of the monovalent vaccine of 21 percent -- again, the confidence intervals. The number of cases in the tetravalent group was 27 versus 49 in the S1 group. This difference was significant as well.

Now, Dr. Rennels showed you that the difference between efficacy for S3 disease of the S1 versus a tetravalent vaccine was demonstrated in the U.S. Multicenter study, but we know there were only a small number of S3 cases in that study.

The predominance of S3 cases in this study demonstrates definitively that the tetravalent vaccine is effective against the S3 strain and furthermore, that the serotype 1 is not. After this we discontinued development of the S1 vaccine.

Also consistent with the multicenter trial, efficacy against severe disease was demonstrated in this study. The numbers, rates, efficacy, and confidence intervals are shown again in the same format.

The incidence of disease with a score greater than eight was 18 percent in the placebo group -- 65 of 81 cases; versus six percent -- 22 of 39 cases -- in the RotaShield™ group; the efficacy

estimate is 66. Again, here's the confidence intervals.

The incidence of disease with a score greater than 14 is eight percent -- 27 infants of 81; and about two percent in the RotaShield™ group -- only eight cases; the efficacy estimate is 70 percent; again, the confidence intervals.

And you can also see the reduction of severity of disease in the vaccinated infants who have a case of rotavirus GE despite vaccination. And this is manifest as a reduction in the mean severity score for the cases, a reduction in the number of days with diarrhea, and a reduction in the number of days with vomiting. And all of these are statistically significant. Obviously, that's how you get a reduction in the score.

Now, prior to the completion of the first year of surveillance and before we knew any of the results the study was amended to include blinded follow-up of the cohort of infants for a second year. All the infants had been vaccinated before the '92/'93 season and so this second year of surveillance in the winter rotavirus season in the last months of 1993 represents the disease that occurs in infants older than 12 months.

This graph shows the incidence of rotavirus in the active and placebo groups -- I'm sorry, RotaShield™ and placebo groups. The peak represents the late-1992 epidemic and it shows the high incidence of disease in this epidemic as well as the efficacy of the vaccine.

To the right of the line is the epidemic in these infants in the second year of surveillance -- the same infants. Note that the peak is substantially lower and that the incidence of disease in the vaccine and placebo cohorts is the same.

The low rate of disease in the second year of life in the American Indian infants is characteristic in this population of the rotavirus epidemics, and it has been noted in previous epidemiology studies in the American Indians. It is attributed to immunity acquired in the first year from the high rate of symptomatic and asymptomatic infections, as well as repeat infection, which is much more common in this population as well.

Not shown on this slide is the fact that severe disease in the population in the second year is virtually non-existent in these infants. This is also characteristics of the population. There were only seven cases in the placebo group with a score greater

than 14, and four in the vaccinated group.

Note also however, that vaccination in the first year has no detrimental effect on the second year. That is, the older infants were protected equally by either wild type infection or vaccination in the first year of life.

The critical difference is that 50 percent of the infants who were vaccinated were spared any disease in the first year, and at least 70 percent were spared severe disease in the first year. There is no additional cost to these infants in terms of worsening disease in the second year.

Our conclusions from the study are shown here. First, the results confirm the U.S. multicenter data in that RotaShield™ reduces all rotavirus GE by about 50 percent in infants younger than 12 months, and that efficacy is higher against severe disease.

Second, RotaShield™ was clearly effective in an epidemic of serotype 3 disease in which the monovalent vaccine essentially failed. Third, the incidence of RVGE in the second year of life in these infants is much reduced and the severe disease is virtually non-existent in both the vaccinated and the placebo groups.

Last on the list of efficacy studies that

were sponsored by Wyeth is the Finnish study. This is a randomized, double-blind study of RotaShield™ versus placebo conducted from September 1993 to May or June of 1995, in 2400 infants; which is about 40 percent of the birth cohort in the district in which the study was performed.

Key differences in this study are that dosing was at two, three, and five months, and it was continued during the first rotavirus season. Most important, the primary endpoint was severe rotavirus gastroenteritis and this was defined prospectively in the protocol as a case with a score greater than ten.

This study was designed and the sample size was estimated to show an 80 percent reduction in severe disease. The secondary endpoint was RVGE of any severity, and additional analogies included the need for medical attention at the local health clinics, at a physician office, or at the hospital, either as an inpatient or an outpatient.

Dr. Timo Vesikari, a professor of Virology at the University of Tampere, and his staff of physicians and nurses, organized and administered the study from the University of Tampere. Enrollment, surveillance, data recording, and medical care for the infants took place in the 99 well baby clinics which

constitute the pediatric health care organization in the Tampere health district.

This is a system of infant care which is well-known for excellent compliance with vaccination, as well as follow-up for well baby visits, and record keeping for childhood illnesses. This study was also recently published in The Lancet.

First, I need to review the dosing. In the U.S. studies, recall that we planned that the infants would complete the vaccination -- all three doses -- before the start of the rotavirus epidemic. In this study, enrollment and vaccination occurred before, during, and after the first season rotavirus epidemic, which is how RotaShield™ is most likely to be given in real life.

This slide shows the monthly recruitment of infants starting in September of 1993; these smaller blue bars represent the monthly incidence of rotavirus in the two years. Here is the first season; here is the second season.

This shows dosing in relation to the season. For example, the group of infants completed vaccination before the first season and they were followed for two seasonal epidemics. This group provides true second-season efficacy information --

and you'll see that in a minute.

This group of infants began the series before or during the first season, completed the series during the season -- the first season -- and were followed therefore, for part of the first season and all of the second season.

The third group began and completed vaccination before the second season and thus were followed for one season only.

The primary analysis includes all infants who completed the doses and met the protocol criteria, regardless of when they were vaccinated with respect to the first season, or in which season the episode occurred.

As in previous studies, the efficacy period began two weeks after the first dose -- I'm sorry, two weeks after the last dose was given. Only one episode per infant was counted in the analysis.

Finally, in this study, the RotaShield™ two, four, six schedule was changed to two, three, five months to better adapt to the Finnish vaccine schedule. The DTP schedule in Finland was three, four, five months, and the Hib schedule was four and six.

What that means is that infants were likely

to receive one or more doses of RotaShield™ and DTP together. However, there was no requirement or restriction on the co-administration of DTP.

Here are the results: 2,282 infants completed three doses; 2,274 -- or 95 percent -- 1,146 in the placebo and 1,128 in the RotaShield™ group were included in the primary analysis. There were 1,818 GE episodes -- 1,293 occurred in the efficacy period starting two weeks after the third dose -- and 1,256 had stool samples for a collection rate of 97 percent.

There were 226 cases of RVGE in the two years of the study, and 100 of these met the criteria for severe. The primary per protocol analysis -- that is, regardless of the time of vaccination relative to the first or second season -- in all cases within the efficacy period in either the first or second season, shows an incidence of eight percent of severe disease in the placebo group -- that's 92 cases -- versus one percent in the vaccinated group -- or about eight cases -- for an efficacy of 91 percent against severe rotavirus gastroenteritis. The confidence intervals are 82 to 96 percent.

Now moreover, in this study in contrast with the American Indian study, the incidence of rotavirus

disease in the older infants in the second year is higher, and severe disease does occur in this group. This slide shows the efficacy of vaccination in the second year for infants who received all three doses before the beginning of the first seasonal epidemic in late 1993.

This is a somewhat small cohort but nevertheless here are the data. Severe RVGE is reduced from 11 of 82 in the placebo group to two of 85 in the RotaShield™ group for an efficacy of 83 percent. And this is consistent with the results that we saw for the overall study.

These results for the second year follow-up in the older infants are also consistent with the efficacy results we observed in the second year from an earlier multicenter study at a lower dose of vaccine. These results were published in JAMA and they were included in the application.

Finally, the secondary endpoint of rotavirus GE of any severity is shown here. This slide shows the number of cases, the rates, the efficacy, etc., and the confidence intervals. Efficacy for all infants, all cases in the efficacy period at season 1 or season 2, regardless of the time of vaccination, is 68 percent.

Note that here as in the U.S. studies, as we've said, the estimate of efficacy against severe disease is higher than the point estimate of efficacy against any disease.

Back to severe disease now, the reduction in severe disease is seen in the analysis of the individual parameters as I showed you for the American Indian study and as Dr. Rennels showed you for the U.S. study -- the multicenter study.

There was a reduction of about three points in the mean score, a reduction by about a day in the duration of diarrhea, and reduction about a day in the duration of vomiting. And all of these are statistically significant.

There's additional information here as well. As a consequence of the decrease in severe cases, fewer of the vaccinated infants required medical care even if they were infected with rotavirus: 78 versus 14 for any medical intervention; 42 versus 13 for a physician visit; 23 versus one for a hospital outpatient clinic; and 13 versus zero for admission to the hospital, which is the hallmark of the most severe disease as Roger discussed with you.

This column shows the efficacy estimates and the confidence intervals for all of these parameters.

I want to remind you. The decision to visit the physician or the clinic or admit the infant to the hospital, was made while the parents, the study staff, the physicians were all blinded to the treatment assignment, the cause of GE was not identified, the score was not known.

The duration of illness, the number of episodes of diarrhea or vomiting were known, but the score wasn't derived until after the study was completed and the database was closed. So you should consider the score and the assessment for hospital admission or medical intervention independent.

Finally, in this study it was possible to determine the serotype for 214 of the cases -- 193 of the cases were caused by serotype G1, 21 cases were caused by serotype G4. These data were analyzed for the secondary endpoint, RVGE of any severity, and showed that vaccination prevents both serotype 1 and serotype 4 disease; the efficacy of 70 percent and 76 percent respectively.

These results from Finland demonstrate the RotaShield™ protects infants against severe RVGE, and they also show that as a consequence of vaccination, fewer infants are seen in the medical clinic or hospitalized for RVGE.

Moreover, RotaShield™ is effective against serotype 4 as well as serotype 1 rotavirus, and in infants vaccinated by the age of about five months, immunity lasts into the second year of life.

I want to summarize the conclusions from all three studies. First, recall that efficacy was demonstrated in three, randomized, placebo-controlled studies. Second, the levels of efficacy are consistent across a range of geographic and socio-economic settings including U.S. private practices, U.S. clinics, American Indian health centers, and Finnish well baby clinics.

The incidence of RVGE is reduced by at least 50 percent in the U.S. studies and 68 percent in Finland. Protection against severe disease was as high as 80 percent in the United States and up to 95 percent in Finland. Protection was demonstrated for two seasons in Finland -- and this is consistent with the results of a U.S. study performed with a lower dose of the tetravalent vaccine.

Protection against all the serotypes of rotavirus has been demonstrated in the program. I've shown you three serotypes: serotype 1 in all the studies, serotype 3 in the American Indian study and in the U.S. multicenter study, serotype 4 in the

Finnish study. Serotype 2 was covered by a Brazilian study which is also in the application.

Dehydration was reduced by 100 percent in the U.S. multicenter study. The Finnish study showed a 100 percent reduction in the need for hospitalization. The need for medical intervention was reduced by 73 percent in the U.S., and the duration of illness was significantly reduced in all the studies.

The last section concerns the safety of the vaccine. The most important goal of the safety analyses was to demonstrate that RotaShield™ does not cause the disease it is intended to prevent. We therefore anticipated and looked very carefully for the symptoms we know result for wild type infection, that is: fever, vomiting, diarrhea, and the secondary symptoms that often accompany fever.

The placebo-controlled studies established the reactogenicity profile of the vaccine. The non-placebo-controlled studies include over 4,000 additional infants and these data in the larger sample verify the absence of the important, rare but more serious side effects, that could occur.

Safety information on RotaShield™ comes from the studies shown here which are listed by number

rather than title -- a total of 9,170 infants in all the studies sponsored by Wyeth in RotaShield™; 4,430 in all the placebo-controlled studies; 2,032 in the U.S. placebo-controlled studies; and 4,740 in the non-placebo-controlled studies.

These cohorts included male and female infants and they were equally represented in the active and placebo groups in all of the studies. White infants -- these columns -- comprised the majority in the studies; Black infants about ten percent of the database in all trials; American Indians about 20 percent of the database. There were a small number of Hispanic infants. If we looked at this carefully we will see that the placebo-controlled studies are balanced by race.

The safety data from all the studies were pooled for these analyses and I'm going to show you the pooled data and I'm going to show you the results from some of the individual studies. First, we need to review surveillance again.

The most critical safety surveillance period was the post-dose reactogenicity period which is the time during which the live virus is present. For days one through five following each dose parents were instructed to complete a diary card.

This had to note the number of stools, the presence of vomiting, as well as the level of activity of the infant, the appetite, and respiratory symptoms of cough, wheezing, or runny nose.

The parents were also instructed to take the temperature of the infant at least once per day and more frequently if the infant had a fever. Axillary temperatures were taken in the United States and rectal temperatures in the American Indian and Finnish studies.

These instructions at the time of vaccination were supplemented by alternate-day phone calls to the parent during this period to assure completion of the diary cards, and by home visits in the American Indian study for the same reason.

The primary reactogenicity symptoms were derived from the diary card information. Vomiting again, was defined as the forceful expulsion of gastric contents. The incidence of diarrhea was derived from the parent's reports of the number of loose stools per day using the same definition as for the efficacy surveillance.

Fever was defined as a temperature greater than 38 degrees Centigrade -- that's 100.4 Fahrenheit. High fever was defined as a temperature greater than

39 degrees Centigrade or 102.2 degrees Fahrenheit.

In this database, fever is the most common symptom following vaccination. This slide shows the percentage of infants with fever after each dose in the placebo and RotaShield™ groups in all of the different studies. The significant differences are highlighted.

In the pooled database for all studies, the incidence of fever is the same in both groups. However, in the placebo-controlled studies, fever occurs more frequently in the RotaShield™ group after doses 1 and 2. After dose 2 note that the difference between the groups is very narrow but the result is still statistically significant. There is no difference after dose 3 in the incidence of fever between RotaShield™ and placebo.

I want to focus in more detail on dose 1. Look at the data now. There is an excess of fever of about 15 percent in the placebo-controlled studies. Most of this however, is due to the Finnish study. The excess fever rate in the United States' studies after dose 1 is about four percent, but it's 26 percent in the Finnish infants.

After dose 2 the increased incidence of fever in the vaccinated group is driven by the results

in the American Indian study in which a fever of 38 degrees Centigrade was more frequent after dose 2 rather than after dose 1. In the Finnish study they're the same.

The rate of high fever is much lower in these studies. It's equivalent between the groups for all studies, but there's an excess of one percent in the placebo-controlled studies but after dose 1 only. This is statistically significant and it's again driven by the results of the Finnish study as shown here.

There's no difference in the U.S. placebo-controlled studies. There's no difference in the rate of high fever after dose 2 or dose 3 between the two groups.

Diarrhea occurred in both groups in an equal rate in the five days following vaccination in the pooled database for all studies, and in the U.S. placebo-controlled studies. The Finnish data are separate here because the data were not collected as stool counts greater than three per day, but rather as diarrhea assessed by the parent as present or absence.

Note that the incidence of diarrhea is low in both the placebo and the vaccinated groups in the Finnish study, but there is a two percent excess of

diarrhea after dose 1 in this study.

Vomiting was equal in the vaccinated and placebo groups for all studies, and for both the U.S. and Finnish placebo controlled studies analyzed separately there are no significant differences on this whole slide.

Secondary reactogenicity symptoms are shown here. After dose 1 there's a statistically significant increase in the incidence of decreased appetite, irritability, and decreased activity. These are likely secondary to fever in these incidents -- remember this is the entire placebo-controlled database. There are no significant differences in the rates for wheezing, coughing, runny nose, or abdominal cramping.

Safety surveillance was continued throughout the study but after the post-dose period this was limited to reporting any adverse events rather than soliciting reports of specific vaccine reactions. During the post-dose period only adverse events different from the reactogenicity were recorded. This include otitis media and other inter-current illnesses.

The only other recording was supposed to be for severe reactions such as severe diarrhea, and

these were then recorded as adverse events. This worked generally well to keep adverse events separate from reactogenicity, but in some cases mild reactions from the post-dose period were recorded as adverse events.

During the inter-dose and the efficacy periods, parents were asked at the subsequent visits or by telephone to recall whether the infant had any adverse events or inter-current illnesses. After the post-dose period they were not asked to record these on a diary card, nor were they asked specifically to take the temperature of the infant.

Mild and common childhood illness such as diaper rash were excluded from reporting in order to make the database more manageable. The infants' clinic charts were reviewed by Wyeth-Ayerst monitors; hospitalization and medical visits were recorded and monitored for all infants throughout the study.

And in the American Indian study the adverse events profile, including the inter-current illnesses, the medical visits, and the hospitalizations was verified by a post-study review of 100 percent of the charts from the Indian Health Service by the study staff from Johns Hopkins.

Finally, the analysis of the adverse events

was performed for the 30-day post-vaccine period as well as for the entire study period, and the results are concordant -- and I will show you only the 30-day data.

The most common events are not surprising. These are inter-current childhood illnesses: otitis, conjunctivitis, cough, bronchitis, eczema, rhinitis, etc. None of these are observed more frequently in the RotaShield™ versus placebo group. All of these are not significant.

Fevers: two percent in the RotaShield™ group versus 1.1 percent in the placebo group. This difference is statistically significant. We already know from the reactogenicity data which I showed you, that fever is more frequent in the post-dose period in the vaccinated group.

Now, these data were not to include the post-dose fevers but in some cases they were included; therefore this difference in fever appears to be explained by the increased incidence of fever in the post-dose period. Nevertheless, we reviewed the case records for all of these fevers in the RotaShield™ group to confirm that none of them were associated with concurrent serious illness.

There were seven infants who died in the

RotaShield™ studies: two of these were in the placebo group and five were in the vaccinated group. The difference in numbers is not statistically significant. For all of the seven infants death occurred more than one month after the vaccine was administered. The proximate cause of death could not plausibly be attributed to vaccination.

This slide shows the causes of death in the time after vaccination. There were three deaths from sudden infant death syndrome: one in placebo, two in the RotaShield™ group. An infant died of meningitis, an infant died of respiratory arrest, there was an accidental injury in the U.S. studies, and in the placebo group in Finland there was an accident injury. All of these as I said, one month or more after vaccination.

On the report of the U.S. study, the multicenter study by Dr. Rennels, who told you that there were two infants who were hospitalized in the post-dose period with diarrhea and a rotavirus positive stool. Based on this study alone we cannot be sure whether this represents a true risk of vaccination or a chance association.

The rotavirus vaccine strains shed in the stool may or may not be the cause of the diarrhea.

Moreover, the study wasn't large enough to distinguish this low incidence of hospitalization in the vaccinated group from placebo.

Now, this is obviously an important issue. Our data indicate that reactions to RotaShield™ are mild and self-limiting; therefore in the larger database we undertook several analyses of hospitalization and medical intervention in the post-dose period.

Now first, all hospitalizations for the entire study period were tabulated for all studies and there were no excess hospitalizations in the RotaShield™ group over the entire study period. I want to focus however, on the post-vaccination period.

Hospitalization within the post-dose period for any cause was analyzed for all of the placebo-controlled studies. Hospitalization for gastroenteritis within the post-dose period was analyzed for the placebo-controlled studies and for the entire safety base sponsored by Wyeth, and including the two studies performed by the National Institutes of Health in Venezuela.

Hospitalization for any febrile illness within the post-dose period was analyzed for the Finnish study. Finally, the use of medical resources

short of hospitalization in the post-dose period for any cause, was evaluated for the three efficacy studies.

First, hospitalization for any cause in the post-vaccination period in the placebo-controlled studies is not different for the placebo and RotaShield™ groups. Each study is shown here separately. The total number of infants is 21 in the RotaShield™ group and 18 in the placebo group. There is no statistically significant difference between the totals or between the numbers in the individual studies.

DR. FLEMING: Excuse me. Can you go back to that slide?

DR. CAMARDO: Sure, I can.

DR. FLEMING: Weren't there 13 hospitalizations in the placebo group that you had reported earlier, related to rotavirus?

DR. CAMARDO: No, that was dehydration.

DR. FLEMING: I thought you were talking about hospitalization for any cause here?

DR. CAMARDO: No, we're talking about in the seven days after vaccination -- only in the seven days after vaccination, not throughout the whole study period.

DR. FLEMING: So at some point -- could you show us at some point, the hospitalization, post-randomization for the two cohorts?

DR. CAMARDO: You mean for the entire study period?

DR. FLEMING: Yes.

DR. CAMARDO: You know, I don't think I have -- I made have that slide and I don't think I brought it. The numbers were six --

DR. FLEMING: Can you get it for us at some point?

DR. CAMARDO: Well, I can tell you the numbers were between six and seven percent for both groups. That's all I can show -- I can tell you that. I know that were the data because we were intending to show it and I decided it was a little too much. But does that answer the question?

DR. FLEMING: I'll follow-up. You can keep going.

DR. CAMARDO: Okay. But I just want to -- this is just the post-dose period. The idea here is, was there an increase that, you know, you could plausibly attribute to vaccination because it was proximate to the vaccination.

DR. FLEMING: Although, if that's the

philosophy why not also include those during the dosing period?

DR. CAMARDO: Well, we could do that but we don't see any difference really, in that either -- except in the Finnish study in which we saw a difference that favored actually, RotaShield™, which I showed you. We're going to need, I guess, to talk about it a little more.

Let me go to the next slide. Now, in the entire database there were only few infants who were hospitalized for gastroenteritis post-vaccination. This is any kind of gastroenteritis but in fact, you would isolate RV positive stool from a lot of these infants, so we've included everyone in the post-dose period.

The data shown here in these four rows show the rate of hospitalization for gastroenteritis for placebo-controlled studies under the Wyeth IND, the placebo-controlled study including the NIH Venezuelan study, all the Wyeth studies -- that's the number you've heard a number of times, including the non-placebo-controlled studies -- and all the studies which include the Venezuela study.

This shows the number of cases, the denominator, the rate per 1,000, the CI for the rate,

the relative risk, the CI for the relative risk, but the PI value for Fisher's exact test for the comparison of the rates.

In the Wyeth placebo-controlled study the estimate of relative risks for hospitalization for gastroenteritis in the RotaShield™ group is four, but in fact the actual risk could be as low as half the placebo group, .45, or 36 times as high, with the p-value as .22.

As we add more infants to the analysis any estimate therefore, becomes more reliable --

DR. MALDONADO: Excuse me. I'm sorry, but I thought you said the p-value was for the Fisher's exact, not for the relative risk.

DR. CAMARDO: The p-value is for Fisher's exact for the rates, yes.

DR. MALDONADO: So it's not the relative risk, p-value.

DR. CAMARDO: No. I made a mistake, then. Yes, I misspoke. It compares the rates; it's the Fisher's exact test to compare the rates. The relative risk is only expressed in terms of the confidence intervals. I practiced and I'm going to get that right; I just made a mistake, sorry.

As we add more into it, the analysis becomes

more reliable and the relative risk decreases. In the last case it's decreased to less than one, the p-value increases to above .5.

Now, we're certain about the number of cases in both the placebo and the non-placebo-controlled studies because as I told you, monitoring for hospitalization was diligent and complete for all the studies in the U.S., Finland, and Venezuela, and we've reviewed the database and the hospital summaries numerous times.

These analyses suggest no definitive increased risk for hospitalization due to gastroenteritis in the RotaShield™ group in the week post-vaccination.

Now, in the Finnish study, given the higher incidence of fever which one might argue could itself require hospital admission for evaluation of the infant, we analyzed data for hospitalization for any febrile illness in the post-vaccination period. The results show first a very low rate of hospitalization for fever and no difference between the RotaShield™ and placebo groups after any dose. And as you recall, it's only the first dose that showed a difference in the fever rate.

In addition, we analyzed the use of medical

resources short of hospitalization, first in the American Indian study. The use of medical resources in the post-dose period is relatively high. In fact, the mothers -- the parents are encouraged to visit the clinics afterwards but there's no difference between the RotaShield™ and the placebo group in the use of the local health clinic after any dose.

For the U.S. multicenter study we have data for the combination of fever and medical visits. This is presumed to be for evaluation of fever. The incidence was low and there is no significant difference between the two groups after each of the three doses. Recall that Dr. Rennels showed you no difference in the fever rates in the post-dose period in the RotaShield™ or placebo cohort in the study.

DR. FLEMING: So is that -- just to go back -- is it 15 hospitalizations versus 12?

DR. CAMARDO: These aren't hospitalizations; these are visits to the physician.

DR. FLEMING: Visits to the physician.

DR. CAMARDO: Yes, sorry. Finally, the is the Finnish study. Medical intervention in Finland has different tiers. There's a hospital outpatient clinic, there's the private physician, and there's the local health care center. We analyzed them separately

after dose 1 only, which was the only dose for which post-vaccine reactions were higher than placebo.

There's no significant difference between the groups for the categories of outpatient clinic and private physician, however, visits to the local health center were more frequent in the RotaShield™ group and the p-value just reaches statistical significance.

Now, just to remind you, these are the well baby clinics. They were established in Finland to handle common, minor problems. This is the most primary level of care and these were the study sites that we recruited to enroll the infants.

These analyses show that there is no excess hospitalization in the post-dose period. There was no excess hospitalization for post-dose fever or post-dose gastroenteritis. The use of medical resources short of hospitalization in the post-dose periods is the same for both groups: in the U.S. that's the multicenter and the American Indian study.

In the Finnish studies in which there was a higher rate of fever after dose 1, there was slightly more frequent use of the local health clinics for the post-dose period, but after dose 1 only.

Now, the last section concerns administration of the vaccine in breastfed infants and

the co-administration with other vaccines given to infants on the same monthly schedule. I want to speed up a little bit here because I don't want to get pulled off.

There was a concern that breastfeeding at the time of vaccination may reduce RotaShield™ take and efficacy, perhaps related to the secretion of rotavirus antibodies in milk. Data from the U.S. multicenter study were analyzed in the subsets of breastfed and non-breastfed infants. Note this is a post-hoc rather than a randomized perspective analysis.

The subsets were defined as infants breastfed at some time during the dosing period or breastfed not at all during the dosing period. The results shown here for the two groups indicate that there's no effect on efficacy regardless of whether the infant is breastfeeding.

Finally, in the U.S. RotaShield™ is scheduled at the same time as DTP-Hib vaccines and oral polio vaccine, and it was therefore necessary for us to demonstrate that the addition of RotaShield™ to the schedule does not interfere with the immune response to these vaccines.

This is a double-blind, placebo-controlled

study to compare the immune response to DTP-Hib in infants who receive these vaccines in combination with RotaShield™ or placebo. Infants received tetramune and RotaShield™ or tetramune or placebo at two, four, and six months. Antibody titers to the four vaccines -- that is, DTP-Hib -- were measured at one month post-dose 3.

This slide shows that the percentage of infants with protective titers to Hib, Diphtheria and Tetanus are similar for the placebo and RotaShield™ groups. I have more detailed data if you're interested in seeing that later.

Second, the antibody titers to these three components are similar as well. This is RotaShield™, placebo, RotaShield™, placebo, etc. And this final slide shows compatibility with Pertussis. These are the five components of the Pertussis vaccine which we measured and the antibody titers are the same -- very close -- for the RotaShield™ and placebo groups in the study.

Finally, data from the U.S. multicenter study were used to show that RotaShield™ does not interfere with the response to oral polio vaccine. Protective titers to the three polio serotypes were measured in infants who received two doses of OPV and

received these two doses of OPV at the same time as two doses of RotaShield™.

Seroconversion is quite similar in the groups for serotypes 2 and 3. This is the polio serotype -- percentage of infants with seroconversion of polio. There is a small decrease in the RotaShield™ group in the serotype 1 response, but this is not significant.

In infants who received all three doses of OPV and three doses of RotaShield™ together, seroconversion is 100 percent to all three polio serotypes.

My summary is as follows. RotaShield™ is safe and well-tolerated. Reactogenicity is essentially limited to low-grade fever after the first dose. There's no indication from the database that RotaShield™ causes fever and diarrhea of severity high enough to require hospitalization.

Some vaccinated infants were brought to the local health clinic in the post-dose period in the Finnish study. RotaShield™ can be administered to infants who are breastfeeding and there is no effect on the efficacy of RotaShield™.

Finally, RotaShield™ can be administered at the same time as DTP-Hib and/or polio vaccine, and it

does not interfere with the immune response to these vaccines.

And I'm sure you know I did all this work by myself with no help from anybody and I want to take all the credit. I wanted to give credit to the people who have worked on this vaccine at Wyeth-Ayerst for the last -- it's approximately ten years and for some of them that represented really a full-time job for that time.

And I also want to extend my appreciation for some excellent help from the Wyeth-Lederle colleagues that joined us in the last few years of the vaccine. I also thought that if I put these names up in public they wouldn't escape and leave me to answer questions by myself up here.

CHAIRPERSON FERRIERI: Thank you. We'll have the conclusions now from Dr. Paradiso.

DR. PARADISO: Thank you, Joe. Thanks for putting my name on that last slide; I did the least work of all those people.

As you have seen and heard, a large safety and efficacy database has been accumulated for the RotaShield™ vaccine. As I mentioned earlier, a fourth efficacy trial was performed in Caracas, Venezuela, using RotaShield™ under an NIH IND. This

was the Ketchman study trial in which 2207 infants in Caracas, Venezuela, received either three doses of RotaShield™ or placebo vaccine at two, three, and four months of age.

Those children were followed up for between 19 and 20 months after vaccination, and the efficacy outcomes that were recently reported in The New England Journal of Medicine can be seen here.

Against severe rotavirus disease using the same definition as in the U.S. studies, the efficacy against rotavirus gastroenteritis was 88 percent; against dehydration associated with rotavirus it was 75 percent; against hospitalizations for rotavirus, 70 percent; and against overall diarrhea was 48 percent in this study.

The next slide shows that this study in Venezuela gives data that's very comparable to the data that we've seen in the other three studies that have been reported and that are a part of the Wyeth-Ayerst IND.

And I think it's significant to note that the study in Venezuela gives us our first glimpse of the potential for this vaccine in a developing world setting in Venezuela, where clearly the disease and the population are different. We are currently

working with the WHO to test this vaccine in other developing countries around the world, including in Africa and Asia.

I conclude by saying that we have demonstrated that the data shows that RotaShield™ is efficacious in diverse populations and consistent with the efficacy associated with a natural infection, anti-mucosal pathogen. The extensive safety database shows the safety of this vaccine when given at two, four, and six months of age, and the data shows that we can manufacture it consistently for use in infants.

Thank you.

CHAIRPERSON FERRIERI: Thank you very much for a comprehensive presentation. We have a few minutes left now for questions from the panel for anyone from the sponsor. Dr. DuPont.

DR. DuPONT: I want some information about the febrile reactions to the vaccine. Were these single temperature elevations or in any case were these sustained for some period of time?

DR. CAMARDO: I'm going to actually show you a backup slide. I'm going to need a few minutes to look for it.

DR. DuPONT: Okay.

DR. CAMARDO: We actually looked at the

duration of fever, so that's what I'm going to be able to show you. And I have the American Indian study -- I think it's slide 12. We also have that for the U.S. multicenter study, but the answer is, they're generally one day. But I'll show you.

DR. DuPONT: One day or at one measurement?

DR. CAMARDO: Well, all we have is one day. I can't tell you whether it's one measurement. This is the number of infants with fever by duration. This is the American Indian study. Remember in that study fever occurred after the second dose.

This is the number of infants with fever greater than one day -- of one day, two days, three days, four days, five days duration for low-grade fever and high-grade fever in the RotaShield™ and placebo groups.

I can't say that there's, you know, that no infants had longer duration fever, but the difference between the tetravalent and the placebo groups is not significant; meaning there is no difference. Most of this is one day. And if you look at the -- I think that fevers higher then 39 are more important, and in fact, there are virtually none greater than one day.

I do not think that I can answer whether this is less than one day, but I might be able to --

yes, I can't. Is that okay? And now the U.S. multicenter study is exactly the same. The numbers are different but -- I won't show you just to show I made a backup slide, but it's the same.

CHAIRPERSON FERRIERI: Dr. Modlin, you had a question.

DR. MODLIN: I have several questions but I'll ask just the most important ones now.

CHAIRPERSON FERRIERI: Thank you.

DR. MODLIN: While we're on the subject of fever, have you done any analysis that looked at the risk of fever based on the age at which the infant was enrolled in the study? In other words, when they received their first dose. The age range of six to 22 weeks, is there any difference between the 6-, and 7-, and 8-week-olds compared to the 18 and 20 and 22-week-olds when they get their first dose of vaccine?

DR. CAMARDO: Yes, could you call up the slide from the histograms -- slides 7 and 8 -- and just while he's doing that, we actually did a cut by the median age and there is a high rate of fever in the older infant; that is, older than the median age which was 11 weeks. This is not surprising. We saw it in earlier studies; we saw it again in these studies.

We then did another analysis looking at different -- you know, a somewhat more precise analysis of the age: one to two months, two to three months, three to four months, four to five months. This is the age at first dose. These are all the placebo-controlled studies including Finland, which contributes most of the fever data.

This shows the percentage of subjects with fever and this shows the percentage of the number of subjects here -- these lines here show the number of subjects who were actually in the age group that contributed the data. And I don't have p guides but I'm not sure that's really what you need.

Really you need to just look at the fever rate. In the RotaShield™ group it's 15 percent, 20 percent -- it goes up to 30 percent three to four months. It seems to stay in the 25 to 30 percent range; it doesn't get any higher. That's consistent with what we saw. And the median age was 11 weeks so this is consistent with the other analysis.

I think that -- we concluded that the fever rate is somewhat higher in the older infants and it's what we saw in a single dose study where we specifically randomized younger and older infants to RotaShield™. But it doesn't seem to keep getting

worse. And this is high fever which shows a similar, you know, obviously it's a similar incidence. Is that --

DR. MODLIN: Yes, thank you.

CHAIRPERSON FERRIERI: If you have some other brief questions now might be a better time to ask John while he's able to boot up all the data rapidly. All right. Do you have any other quick questions that you want to bring up?

DR. MODLIN: Yes. I realize the primary efficacy analysis was done on infants that had received three doses of vaccine, but do we have any information from all these studies on efficacy of infants who received fewer than three doses of vaccine?

DR. CAMARDO: Yes, we do. And I don't think all of that is in your package. Now, I can call up the data or I can just tell you. We did two other kinds of analyses for the U.S. multicenter and the American Indian study and the Finnish study.

We did an analysis that just included all randomized infants. The good, old-fashioned, anybody who was randomized is in the group -- actually in the group they're randomized to. Now, that includes infants who didn't get all the doses, didn't get two,

three, etc., weren't in the dosing windows.

The efficacy period there still begins two weeks after the last dose. The efficacy results are the same as the primary analysis; they're the same. I can show them to you if you want but they're the same.

Do you want to see them? I mean --

DR. MODLIN: I'm not quite sure what you mean by "the same". Do you mean the efficacy --

DR. CAMARDO: I'll show you. Let me show you the intent-to-treat analysis which we did.

DR. FLEMING: Which is different from what you were just describing, right?

DR. CAMARDO: Yes, but let me show you the -- now, these are all randomized infants, and these are the cases and these are the relative efficacy. I don't remember the exact number but I think the efficacy was 51 percent. Peggy, do you want to help me out here?

DR. RENNELS: Yes. In the primary analysis, RotaShield™ efficacy was 49 percent -- a one percent difference there -- and for serotype 1 it was 54 percent. So again, just one percent difference.

DR. CAMARDO: Now, I realize this is important so if it's not answering your question go

ahead. But this is all randomized infants: one, two, or three doses. Now, if you ask me for one dose or two doses the answer is going to be, there aren't that many children, in fact.

DR. FLEMING: Isn't the intent-to-treat analysis here 68 versus 107 events and a 30.32 efficacy as reported in our book?

DR. CAMARDO: That's a different analysis.

DR. FLEMING: That's the intent-to-treat?

DR. CAMARDO: Well, unfortunately, intent-to-treat was used to describe different things. I think the one you're using is --

DR. FLEMING: All randomized; from times zero.

DR. CAMARDO: And what about the case accrual? From times zero or from two weeks after the dose?

DR. FLEMING: From times zero.

DR. CAMARDO: Okay. For 312 what you have is 32 percent efficacy for overall, but it's a typographical error. It's 39 percent, not 32 percent, okay? And I just -- sorry, but those do happen. And in fact -- oh, good, you called it up.

(Laughter.)

This is very dangerous but I know that the

FDA is going to check all of this stuff out so don't worry.

CHAIRPERSON FERRIERI: We don't doubt that at all.

DR. CAMARDO: I'm sorry?

CHAIRPERSON FERRIERI: We don't doubt that point at all.

DR. CAMARDO: What, that it's dangerous?

CHAIRPERSON FERRIERI: No, that they will check you.

DR. CAMARDO: You know, we do see additional cases which -- some of which are post-dose cases, some of which are cases that occurred in the inter-dose period and probably represent, you know, cases that occurred before the full 3-dose series.

We did also look at severe disease though, and I think we should show that because, if you're concerned about this difference in efficacy, when you look at severe disease the efficacy really doesn't change too much. And this is all randomized infants from the day they got the vaccine.

DR. FLEMING: ITT and per protocol are similar for severe, which is really reassuring. They're not necessarily similar for the protocol-defined, primary endpoint in the U.S. multicenter

trial: 51/68, we're missing 17 cases; 107/97, we're missing ten. Usually you're thinking, I'm going to drop out those cases that occurred during dosing because the effect hasn't occurred yet.

DR. CAMARDO: That's actually what we're thinking.

DR. FLEMING: But there actually are more cases that we're dropping out with the RotaShield™.

DR. CAMARDO: Yes, now in fact, not only did we include -- and in fact, maybe this isn't correct -- but not only did we include all the cases but we included cases of positive stools that didn't actually meet the definition.

So in fact, there are six of those in the multicenter study. So the actual number here is, if we followed our own rules this number would be 61 or 62, I can't remember -- but for the sake of most conservative we just threw everything in. And parents did send stools and then we looked at the definition now.

You know, we needed to have -- there are asymptomatic road virus cases. We did not want to count those -- doesn't make sense to count them -- but if the parents got two stools a day, collected the stool, we analyzed the stool, it's included. So you

know, just when we do this we have to I think, keep in mind that this probably went overboard. This one.

CHAIRPERSON FERRIERI: Thank you.

DR. CAMARDO: Is that -- I mean, am I answering the question? I'm sorry, I'm really excluding -- I said I was going to ask for help and I'm excluding everyone.

DR. RENNELS: I would say, keep in mind that when you start counting at day zero, any stool that gets collected for any gastroenteritis in the vaccinees may be positive for -- just because of vaccine shedding, also.

CHAIRPERSON FERRIERI: Thank you. Dr. Maldonado, you had a question.

DR. MALDONADO: I just had a question on the U.S. multicenter study when you talked about hospitalizations post-vaccination. And of the five -- I'm sorry, of the three rotavirus vaccine recipients who had fever, vomiting, and diarrhea, did you isolate other pathogens besides -- I know two of them had vaccine virus but did you isolate other pathogens, or did you attempt to? And then I have a second quick question.

DR. CAMARDO: Peggy, that's really a question for you. I know you had the charts. Were

any pathogens isolated from the two infants who had rotavirus stool? I think not, and I'm sure something was looked for, but I think nothing --

DR. RENNELS: In only one child was it looked at and they simply cultured for, you know, sort of the routine bacterial causes and they were negative. That second case actually, although the admitting physician said diarrhea, to the best of our records there was actually only two diarrheal stools, and that one I don't believe got worked up.

CHAIRPERSON FERRIERI: Did you have another question?

DR. MALDONADO: Yes. This is actually a follow-up to Dr. Modlin's question which I think was really kind of looking at the Hib correlate which is, what is the efficacy after each dose, basically? Do you have that data. And again, with Hib we know that first dose doesn't count, second dose is better, and the third --

DR. CAMARDO: I can't tell you. In the entire database of placebo-controlled studies we had 54 infants who only got two doses. It's just not enough to tell you -- to give you an answer. It would be just specious to draw a conclusion. I mean, these are the number of infants: 26 in Finland, 18 in the

American Indian, 9 in the U.S. multicenter study. I think I added it right -- it's actually 53.

So there really aren't enough and there's not enough in an individual study. I mean, you know, you could look at it but I don't really believe we could draw a conclusion that would be valid and then, even it were positive, would allow us to give just two doses and feel comfortable. We really went out of our way to make sure there were three in that protocol and three were followed.

CHAIRPERSON FERRIERI: We have time for maybe two brief questions: Dr. Hall and then Dr. Fleming. And if you're really short, then Dr. Karzon can ask his as well.

DR. HALL: First, going back to the fever just for a second here. I may have missed this. Were any of these children given acetaminophen prophylactively?

DR. CAMARDO: No. We did not advise mothers and fathers to do that. We advised them to treat fevers but not to give prophylaxis. Peggy, that's your recollection as well from the U.S. multicenter study? Some of them might have gotten prophylaxis if they were getting DTP at the same time, but we didn't advise it. We specifically -- I mean, we looked for

fever, so we didn't cover it.

DR. HALL: And you said axillary temperatures were utilized in the U.S. study. Does that mean it was uniformly utilized?

DR. CAMARDO: It was uniformly -- the protocol specified way to take temperatures, yes. In the American Indian study it was rectal temperatures and there was a 91 percent rate of rectal temperatures in that study. In Finland it was rectal temperatures.

DR. HALL: And then I guess the last thing I wanted to ask was about the difference in the growth retardation in the groups that was recorded.

DR. CAMARDO: You mean that -- the borderline statistics -- yes. There wasn't any good way to analyze that so instead, what we did was went back and looked at all the cases. It turns out that what that includes is children -- it includes a lot of different diagnoses, most of which turned out to be children who were in the lower five percentile of the growth curve -- like my daughter is -- and it got in there.

We really couldn't -- we did this with the investigator in Finland as well. We can't find anything in those cases to suggest that there's anything related to the vaccine, and in fact, some of

those were described and included infants who had other serious illnesses -- somewhat serious illnesses at birth that might have contributed, or had injuries.

And in fact, I know we're going to look at this again with FDA because they've requested those forms. But we can't do an analysis. We had to really look at the terms -- look at all the cases.

CHAIRPERSON FERRIERI: Thank you. Dr. Fleming.

DR. FLEMING: To be very brief I'll defer my comments or questions about the heterogeneity of efficacy and safety across studies and about co-administration issues; we can talk about it later.

A quick request and a very quick question. The quick request is, during the break could we get a summary for each of the three trials of the hospitalizations that are due to rotavirus GE, separately by -- I know it's zero/13 for example, for the Finnish trial.

DR. CAMARDO: Finland, yes.

DR. FLEMING: The number that are due to febrile illness for each of the studies, as well as overall hospitalizations, and then the same data for medical visits, hospitalizations. And I'll stick around during the next hour to work with whoever it is

to try to gather that during the break so we can have that this afternoon.

The quick question that I have is, you mentioned that there are eight studies -- there were eight randomized, controlled trials that yielded these 6948 subjects. We've looked carefully at three randomized, placebo-controlled trials.

You've shown us the Venezuela trial, you've said there were -- you referred to three other non-placebo-controlled trials and two other placebo-controlled trials. Was the Venezuela one of those two and are there any relevant data on efficacy and safety from these other four or five studies that we haven't looked at?

DR. CAMARDO: I'm sorry, for the other four or five studies -- no, there really were not --

DR. FLEMING: There were eight studies overall.

DR. CAMARDO: No. I mean we -- no, there are not, really. I mean, I'm showing you the pooled data. The one study you didn't see in detail is this one, which was essentially -- was a one-dose study of RotaShield™ in younger and older infants, and I described the results to Dr. Modlin. There's really nothing else in the database specifically, that we

would want to look at.

DR. FLEMING: So most of the 6948 that don't fall into these three trials are in the three non-placebo-controlled studies?

DR. CAMARDO: Essentially, yes. There were 1500 in the consistency lots, 2700 in the large-scale, just basically safety study. Yeah, those other ones are very tiny. It says it includes the interference, this one-dose study and another small study --

DR. FLEMING: And Venezuela is one of these eight?

DR. CAMARDO: No.

DR. FLEMING: Oh, it's not?

DR. CAMARDO: No, it's not, no. Venezuela is an additional study, and we can see that if you want, but that's an additional study. When I showed you that list with the relative risk on it, the Venezuela study added another 2,500 children to the database, plus there was another study in Venezuela which was about 150 children. So if you put all those studies together that's a much higher number.

CHAIRPERSON FERRIERI: Thank you. Dr. Karzon.

DR. KARZON: I will defer.

CHAIRPERSON FERRIERI: Really? Because

there's time. You can ask your -- you think it will interfere with lunch. Okay, we'll wait then. We're breaking for lunch now. We'll start again at 1 p.m. promptly. Thank you all.

(Whereupon, a brief luncheon recess was taken at 12:10 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:04 p.m.

CHAIRPERSON FERRIERI: We don't have all of our panel sitting at the table yet but I know that will happen very shortly. We will start with clinical considerations. Do you want to start first, Nancy? Okay. Ms. Cherry then, has some administrative issues to present to us.

MS. CHERRY: I would like to mention that some additional conflicts of interest, or potential, or perceived conflicts of interest have come to our attention today, and so there's been quite a bit of checking.

I would like to report, simply disclose that we have looked into some situations with Dr. Maldonado and she is fine to sit at the table and participate. And we also looked into something for Dr. Neal Halsey and because of that we've asked him to sit on the sidelines and he will not be able to participate.

CHAIRPERSON FERRIERI: Thank you, Nancy. I think the sponsor appreciates this and doesn't think less of all the people we are investigating.

(Laughter.)

Nor do I. And Yvonne, you will not be voting as you understand. Okay. Dr. Carbone will

present on clinical considerations.

DR. CARBONE: In the beginning I'll have some brief material just to remind everyone of some of the circumstances surrounding the studies. We are mainly focusing today on 312, 314, and 316 which are defined by the sponsor as the multicenter trial, the American Indian trial, and the Finnish trial. Those we are concentrating on today.

You will see some differences on what we concentrate on and what the sponsors concentrate on. In particular we have certain studies that were submitted specifically for efficacy analysis for the trial, and there are studies that are also available -- that data are available, information are available -- but for various reasons were not actually submitted for efficacy analysis for the PLA, specifically, and we'll discuss those a little bit.

In addition, you'll see some figures today that we recently got within the last week or so, and the committee has not finished a complete evaluation of these figures but we prefer to present them to you since we have this opportunity.

Basically, the studies are selected for use in efficacy for the PLA because they were three doses, 4×10^5 plaque-forming units -- which is the dose

requested for licensure -- and in these cases, these studies, the infants were observed up to 24-and-a-half months after vaccination.

Per the protocol analysis for the sponsor efficacy, monitoring for their protocol primary endpoint began two weeks after the last dose. However, we have asked the sponsor -- we have included intent-to-treat information which -- starting after enrollment, any episode of diarrhea. So that will give us slightly different numbers and I'll discuss those when we get to them.

Just to remind you, stool specimens were collected during all clinical episodes but as you've heard the studies did vary as far as those that were available for typing for present of rotavirus, ranging from about 60 percent to somewhere in the 90 percent of the three trials. And then some specimens went through additional characterization by RT-PCR for serotype analysis.

Just to remind you that the primary endpoint in the multicenter trial and the American Indian trial was simply rotavirus gastroenteritis, and here is the definition once again in a 24-hour period of vomiting, diarrhea, plus the assay for rotavirus.

Again to remind you, in the Finnish study

the primary endpoint was actually severe rotaviral gastroenteritis, which was the previous definition plus a scale of -- actually it's greater than ten which means equal to 11/20 as determined by the rating scale.

In an analysis of the data it's always important to look at the withdrawals in the study since that can affect the validity of the data. And so these are essentially, all the clinical trials in the United States and the Finnish trial.

At the proper dosage being applied for licensure, the withdrawals were approximately ten percent from the RotaShield™ recipients and 7.2 percent from the placebo recipients. Of course the numbers, the ends were different because this included non-placebo-controlled trials.

If you look only at the placebo-controlled trials in the U.S. in the Finnish studies you can see that the withdrawal rates were seven percent for the RotaShield™ recipients, 7.2 percent for the placebo recipients, and there was no significant difference.

In addition, the adverse reactions specifically, accounted for only .1 percent of withdrawals in both groups. And again, there was no difference between placebo or vaccine recipients.

Some of this information has been presented by the sponsor. I will go through that information quickly and try and only concentrate on the information we have that may differ or is a different type of analysis.

Again, looking at the three trials which were submitted for efficacy for this PLA, fever of greater than 38 degrees and greater than 39 degrees were found to be significantly increased in the first five days after vaccine; as well as in the Finnish study it was reported that diarrhea was significantly increased in the first five days.

And that data is simply illustrated here and this has been presented by Wyeth so I won't dwell on it. But we see that fever actually greater than 38 is seen after dose 2 as well as dose 1.

There were some secondary symptoms that were noted in these infants in the series of placebo-controlled trials and that included decreased appetite, irritability, and decreased activity after dose 1 only, as you've already seen.

Next we will discuss study events within 30 days. Placebo-controlled studies: again fever was significant; greater than 38 degrees C. Another adverse event that we thought was important to look at

was severe gastroenteritis within 30 days of the dose. And these are the individuals who had gastroenteritis -- some very shortly after they got the dose, within about a week; others a little more.

The investigators in each case found -- in both the vaccine recipients and the placebo group, the investigator stated that in one case it was not related and not related two cases in the vaccine recipients. And so probably and possible in one case each.

After any dose, a review of the placebo-controlled studies in the U.S. studies and the Finnish studies were from one month post-study dose to greater than two years in some selective individuals. Again, this evaluation found that fever was significantly increased in those that received the RotaShield™ over the placebo.

In addition, when the analysis was done, congenital anomaly was also found to be significantly different between the vaccine recipients and the placebo. We mention this for completeness.

A review of the specific anomalies seen included extra digits, undescended testicles, and by definition, congenital anomalies are present at birth and the children received the vaccine several weeks

after birth.

So our review suggests that -- this is mentioned purely for completeness' sake and was not felt to be associated.

In terms of serious events, we'll look at hospitalization in all studies and including the placebo-controlled studies, the rates of meningitis, hepatitis, and seizures were evaluated and were in all cases, lower in the vaccine recipients than in the placebo recipients.

Rates of hospitalization specifically for gastroenteritis in the first week after receiving the dose in the U.S. and internationally -- you can see the little signals here that indicate which of these numbers is which -- placebo-controlled studies, there was essentially no difference between rates of hospitalization for gastroenteritis in the first week after receiving the vaccine.

And you see the sponsors presented information about other hospitalization events. Obviously, we're all concerned to evaluate carefully the deaths following any studies like this involving a new agent. And in the placebo-controlled efficacy studies as stated by the sponsor -- this is reviewing what they said -- there were five deaths in the

vaccine recipients, two in the placebo recipients, it was non-significant by Fisher's exact test, two-tailed.

DR. FLEMING: For those -- just, before you go into it --

DR. CARBONE: I have details on what the deaths were, if -- that's on the next --

DR. FLEMING: No, I just thought the denominator --

DR. CARBONE: Certainly.

DR. FLEMING: -- on the five deaths in the RS was for the entire 6700, as opposed to for the 2200.

DR. CARBONE: All five deaths were included in placebo-controlled trials. All right? But in order to do the statistical analysis we need to compare those only to other placebo recipients.

DR. FLEMING: Right. So you're saying the five deaths were all in these placebo-controlled studies?

DR. CARBONE: Yes, yes. And again, you've seen this information as to the cause of death, so the individuals, it varied but none of these were apparently, due to any study material.

This is a subset analysis which was briefly

mentioned by Wyeth in the previous discussion. I want to be clear that this was not a prospective.

This is a post-hoc analysis, but it may reveal some interesting information, particularly in light of the information we have that we're actually getting wild type rotavirus infection early-on in life. Perhaps it's less pathogenic than getting it a little later in life.

So these data are interesting and are being attended to but are as I said, not prospective and perhaps information contained in here requires further prospective analysis.

Basically, the analysis was done taking the median age and looking at the group less than or equal to 11 weeks of age versus the group greater than 11 weeks of age at first dose. And note -- a sidebar on this is that many of the infants who were in the less than or equal to 11 weeks at first dose, by the time they're in their second dose, are greater than 11 weeks.

Days one to five in both groups, greater than or less than 11 weeks, fever was again a significant event. However, in the total study period, in the group less than 11 weeks old there was no significant increase in any other study event in

that group. On the next slide we'll look at the greater than 11 weeks.

Again, this is the same, non-prospective analysis. These are the four analyses that came out showing statistical significance in the groups. Fever as we said before, in the greater than 11 weeks; congenital anomalies we've dealt with before. It's the same issue.

And review of these congenital analysis show none of them related to the vaccine -- receiving the vaccine. However, there was -- growth retardation and failure to thrive were noted, significantly increased in the vaccine recipients -- recipients again using the post-hoc analysis.

In a review of the data, most of the children were stated to be mild -- was the investigator's analysis of the severity of the disease.

DR. MODLIN: Kathy, I'm sorry.

DR. CARBONE: Yes?

DR. MODLIN: What's the difference between failure to thrive and growth retardation?

DR. CARBONE: That's an interesting question because if you look at the actual data, in the Finnish study there seems to be -- growth retardation seems to

be the designation, where there were many in the Finnish group and none -- very few in the American studies.

And failure to thrive is the same in the reverse. And I apologize if I've gotten the countries reversed, but in one of the countries growth retardation seemed to be the favorite diagnosis, and failure to thrive in the other country.

As to how they were defined, I looked this up, and maybe the sponsor would like to say if they have any more detailed information about how it was diagnosed.

CHAIRPERSON FERRIERI: Dr. Camardo.

DR. CAMARDO: Yes. I think what this really is, is a coding anomaly. They're the same thing; they get coded to different costar terms based on whether the physician writes growth retarded or thriving badly, or something like that. And I think they're basically the same.

DR. CARBONE: From my review, I came up with the information that this was basically a physician diagnosis; that --

DR. CAMARDO: Yes, it is.

DR. CARBONE: -- you did not provide them with any criteria.

DR. CAMARDO: That's correct.

DR. CARBONE: Okay. This is -- just to finish up with that last slide again, because of the post-hoc analysis nature, it may suggest that further information would be helpful in these areas.

In terms of the fever which has, at least pretty consistently appeared as a relatively standard, post-vaccination event, I just wanted to be clear it was -- in the less than 11 weeks it's present after the first dose and in the greater than 11 weeks after the first dose. In the less than 11 weeks it's also present on the second dose in significant fashion.

However, fever greater than 39 degrees C -- which of course is a significant medical concern -- was not present in the younger group at the first dose significantly, and was in the older group. However, this group had aged so it is possible that these two events are actually connected.

These children -- many of them are likely to be older than 11 weeks at the time of the second dose. Nonetheless, that the time of second dose, the original group that was less than 11 weeks at first dose also showed fever greater than 39 -- a very small percentage but significantly different.

In terms of safety analysis I'm just going

to present a little information that I haven't heard yet today. These involve two studies in Venezuela. I want to again highlight that these studies for various reasons were not submitted for official efficacy consideration for this PLA but for additional side information.

In the case of the second study there was a protocol change that was during the study and did not meet the IND requirements for use in this PLA. At any rate, we do have information however, on the ability of this vaccine agent to transfer from individual to individual, from these two studies and so for safety data are included here.

Basically, rotavirus was detected and serotyped in 217 stools from children in the 309 VE study -- that's Venezuelan study. Vaccine strain viruses were identified in placebo recipients and in vaccine recipients. So this by definition, suggests that the virus can transmit to the placebo recipients who were not officially administered the vaccine.

However, the vaccine virus was found in very low titers in the stool. Vaccine strains were always detected with a wild type strain, and the report states that this did not -- vaccine strain did not circulate in the community three months after

cessation of vaccination.

I would like to also mention that this is stated in this setting; that virtually all of these are going to be exposed to the wild type as well.

DR. EDWARDS: Could you just comment on the detection with the wild type strain -- the vaccine strains? I'm sorry, both Caroline and I don't understand that.

DR. CARBONE: In every case where they found the vaccine strain they also recovered evidence of presence of a wild type strain -- in the same stool at the same time. And please correct me if I've misstated that. Is that clear now? The stools were --

DR. EDWARDS: Unexplained but clear.

(Laughter.)

DR. CARBONE: We recently got new information that confirms the same finding in the same direction and that is, in the 326 study -- which again, was not submitted for efficacy evaluation but for information provided for safety -- 199 stools were rotavirus positive and then subsequently serotyped; 27 stools contained the G1 and the vaccine strain -- that was 14 percent.

In the placebo recipients they found the

vaccine strain in 13 percent of the placebo recipients in this group, and in the vaccine recipients they found the vaccine strain in 15 percent.

The vaccine strain was at 2 X 10^4 pfu per .5 ml of stool. As stated in the report, it was stated in a 1:10 dilution of stool so I have adjusted this to per ml of stool -- per half-mil, pardon me, of stool.

DR. SNIDER: These are all symptomatic? I mean, these patients from whom the stools were collected were all symptomatic, correct?

DR. CARBONE: My understanding is, the reason the stools were collected is because they had evidence of gastroenteritis. Is that correct?

DR. MALDONADO: And do you have data on how long the virus was shed?

DR. CARBONE: The only data I have on that in my immediate possession is the 309 study where they said it was gone after three months -- three months after the study stopped they no longer could recover the virus.

And to move on to the efficacy information, just to remind the group of the questions of importance I'm going to cover some information about RotaShield™ reducing the incidence of all gastroenteritis, of rotavirus gastroenteritis, of

severe rotavirus gastroenteritis, and rotavirus gastroenteritis in the second season following vaccination.

In terms of the efficacy studies, again we're going to be interested in the three major studies that were submitted for efficacy analysis. This is the study that's the multicenter U.S. study -- is 312; again, the Native American, or American Indian study, 314; and 316 is the Finnish study.

This slide is just to show the relative enrollment and dropout rate of infants who receive three doses versus the number enrolled in all the studies. You can see there was somewhat of an increased dropout rate in this study, but it was similar in both groups -- placebo and vaccine recipients.

I apologize about the busy nature of this slide and I have smaller slides with this information, so if it's not possible at all to see this in the back I can go through it one study at a time. But I'll begin by reviewing them together.

This gets a bit complex. There were three basic, efficacy analyses done. One was a per protocol analysis which essentially was after three doses of vaccine starting two weeks after the last dose was

received.

Then there was an analysis -- and that was done on a per subject basis. Then there was a similar analysis after three doses of vaccine and two weeks that was done on a person-year basis because some of the follow-up times were different in some of the studies.

In the third analysis, thanks to our very good statistician, Dr. Horn, was the intent-to-treat analysis performed by Wyeth that involves after any individual enrolled and any diarrheal episode -- no time requirement. So this is why you'll see several different analysis. And I apologize. It gets complex and I'll try and do the bottom line here.

The bottom line in the first study, the multicenter study, we're looking at efficacy against rotavirus gastroenteritis. And then we can see the efficacy is 49 percent in the original per protocols -- essentially the same or better.

In the person-year evaluation per protocol, these two groups have received two doses of vaccine; that's the ideal world. This is maybe considered intent-to-treat is the real world, meaning anyone who arrives and signs up is evaluated and the efficacy is dropped to 32 percent.

DR. FLEMING: Do you agree that's a typo; that that's 39? Or is that up for question?

DR. CARBONE: Yes, that's the same typo. I got it from the same -- I apologize. Like I said, we're currently reviewing -- but yes, that is 39 percent. Yes, thank you. Okay, so yes, that's 39 percent.

And this maybe perhaps reflects the real world -- use of vaccine. The American Indian studies, again, we see in the per protocol analysis three doses 52; three doses in person years, 54; and 38 in the intent-to-treat. The Finnish study, 83 percent efficacy and 84 percent, in the three doses, 74 percent.

And I noticed on the slide presented by Wyeth it said 68 and in the material I re-reviewed the 68 percent was after both seasons combined. So unless that's incorrect I'm sticking with that 74; that's after the first season, the information you provided us. These are all after the first season.

So that was the efficacy, simply for all rotavirus gastroenteritis. But as been stated before, the efficacy against severe rotavirus gastroenteritis appears to be improved.

And as the sponsor has also supplied some

information that if you just look at the score, the severity score in vaccine and placebo recipients on each of the number of individuals this data was obtained from, in all cases the severity score is reduced compared to placebo in all three of these studies in a significant fashion.

The 316, again to remind you the Finnish study used a different severity scale.

Efficacy analysis is comparable to the previous one we did for all rotaviral gastroenteritis. This is severe rotaviral gastroenteritis. This first line includes the three doses; however this is a per person year evaluation. I've left out the per protocol analysis. It's essentially very similar.

And what you can see in severe rotaviral gastroenteritis as defined by greater than 14 in these two studies because this was -- the protocol was changed to actually go to greater than 14 as the definition of severe rotaviral gastroenteritis. And you can see from the previous slide that 15 was about comparable to ten in the Finnish scale.

And this scale was 11 or greater. This is severe rotaviral gastroenteritis. And taking those definitions of the clinical rating scale, in either after the three doses or the intent-to-treat analysis

is about the same in all cases.

Now, I apologize. This is a typo. That number is 579 but this is the number that we were supplied with and that we are -- again, it's in the hands of our statistician now.

This analysis of all -- because rotavirus is such an important cause of diarrhea in children and because of the fact that all diarrhea in children is not tested for rotaviral antigen and is not clearly diagnosed as rotavirus, the estimation of the protection of this vaccine against all clinical gastroenteritis is an important one because that is essentially what is seen in the home setting.

And in this case the analysis was done between RotaShield™ and placebo. I have a second analysis on the next slide, but here we're looking at specific, clinical signs and symptoms. They're different in many of these studies.

Basically, the common link here is that dehydrating gastroenteritis was identified in all the studies by the sponsor and in all cases there was a significant reduction in dehydrating gastroenteritis in taking all gastroenteritis as comers in all three cases.

Medical intervention for example, is defined

differently in the studies, but in every case whether the severity of greater than eight -- which they consider mildly severe gastroenteritis in these two studies -- there was significant evidence that in many different clinical ratings that in all gastroenteritis there seemed to be effect of the vaccine.

However, this is a subset, non-protocol analysis that was obtained from data provided by the sponsor in very small numbers, doing it in person-years analysis, either after three doses or an intent-to-treat analysis, and the efficacy against all clinical gastroenteritis doesn't fare quite as well in the intent-to-treat analysis using this small subgroup.

In the case of the study 312 -- this is the multicenter study -- after three doses the efficacy against all clinical gastroenteritis was 55 percent. In the intent-to-treat analysis in the same study it was 21 percent. And I would point out the confidence interval here.

In study 314 U.S., which was the Native American-American Indian study, the efficacy after three doses, relative efficacy is 53 percent, and with the ITT, intent-to-treat analysis, was 28 percent. Again, note the confidence intervals.

So in sum, in that analysis I think it's fairly evident that the second -- the severe rotaviral gastroenteritis -- efficacy against severe rotaviral gastroenteritis has fairly good efficacy and that it comes down as you go to all rotaviral gastroenteritis and all gastroenteritis.

Change -- another issue that has been raised is the ability of this vaccine to protect through two seasons. This is a very difficult, actually, point to analyze. Our statistician, Dale Horn, pointed out that there is a change in risk for the population in the second season.

Obviously entering into the study the population is randomized into placebo and vaccine recipient. At that point there's a difference in incidence of wild type infection which will change someone's risk for getting symptomatic, rotaviral gastroenteritis in the second season.

There's also evidence that the vaccine has some efficacy which will change the risk in the second season. At that point for the second season, the populations become non-random and it's somewhat of a difficult point to ascertain.

This is the subjects with rotavirus gastroenteritis during the second season in the 314

study and the 316 study. The multicenter trial was not specifically designed to look at the second season. These were done on a prospective basis and that's why they're included.

As Wyeth has shown you, however, the incidence of disease in the second season in the American Indian trial was very, very low. So these data are very hard to interpret and it's very hard to show significance. And the data as they are show no significant protection in the second season, but there are the caveats I mentioned.

However, in the Finnish study, efficacy in the second season either done three doses or three doses per person subject to three doses per person-year, or intent-to-treat after any dose at any time, all showed efficacy in the 16 percent range.

There was also the study mentioned in 307 -- I'm sorry, 310, pardon me -- which also showed some evidence of significant second season -- 307, pardon me -- which also showed significant -- of the -- 310, pardon me -- 307, which also showed some significant efficacy that's a 3-dose, per person, per subject analysis of 48 percent.

However, that study was not included for specific efficacy analysis because it is not at the

dose being requested. That was the 10^4 dose of vaccine. However the data are very suggestive of second season efficacy and maybe this is a point which we were presenting to the committee for discussion.

Obviously, interference with another vaccine delivered orally is an important consideration. RotaShield™ could be delivered with oral polio vaccine at the same dosing schedule. This was evaluated in 418 recipients for serotypes 1, 2, and 3.

GMT for antibodies to serotypes of OPV were no different, and percentage of subjects with detectable antibody were no different, as was mentioned. After the first dose there was some non-significant difference in serotype 1, but there was no significant difference in all three serotypes but the numbers are small.

Incidence of rotavirus gastroenteritis was not affected by doses of OPV. This is actually a different bit of information because there may be a consideration of the OPV interfering with the rotavirus efficacy -- rotavirus vaccine efficacy. That's a difficult thing to measure from an immunological marker because as stated by the sponsor there is no current, immunological marker for protection from rotavirus.

So looking at the clinical protection of the RotaShield™ against rotaviral gastroenteritis in children who receive simultaneous RotaShield™ and OPV, at least the numbers that we have here show no adverse effect on the RotaShield™ after at least receiving the three doses of the RotaShield™.

The other vaccine which is administered parenterally and not orally like the OPV, was studied in diphtheria, tetanus, and pertussis, the wholesale version and the hemophilus influenzae B conjugate -- 267 subjects. The GMTs were not significantly different between those that received the vaccine and the placebo.

There was no significant difference in antibody titers above the established protective levels for the H. influenzae, there was no significant difference in titers, distribution of titers to pertussis antigens, and 100 percent of subjects in both the placebo and vaccine recipients had protective antibody titers.

Immunogenicity has been covered. We won't deal with this other than to say that the importance of the large efficacy studies in the case of determining RotaShield™'s activity are necessary, particular because there is no current immunological

marker predictive of protection.

This is again, a slightly different slant on some information that were presented by the sponsors that basically confirms that. And that is, that in cases -- in other words, children who had evidence of rotaviral gastroenteritis and children who didn't, if you compared the serology in the children, those who received the vaccine and those who didn't, and had rotaviral gastroenteritis, those that received vaccine or those that didn't and did not have rotaviral gastroenteritis, there is essentially no difference between these two groups. Again, highlighting the lack of a good marker for immune protection against rotavirus.

Issue of serotype has come up. This is a vaccine which contains four different serotypes, and this is just an illustration that in this study which is the multicenter study, it's about 75 percent of the children who are diagnosed with rotaviral gastroenteritis and that were subsequently serotyped, had serotype 1; somewhere in the order of a quarter had serotype 3. So those were the two predominant types in the population: a smattering of 4, a little bit of 2, and several unknowns.

In terms of efficacy, this information has

been presented. I just want to review it. That there was evidence in this same study of efficacy against serotype 1 and serotype 3, but there were insufficient numbers of serotype 2 and 4 in this study to determine if the rates were sufficiently different between rotavirus and placebo recipients.

As you can see there's a reduction in cases here; there's a reduction in cases there. I apologize I left off the end. It's the same number here. But there are insufficient numbers in serotypes 2 and 4.

However, we were recently presented with some additional data. This just in 314 which is the Native American Indian study in the United States. The relative efficacy was 56 percent against serotype 3, so again this supports what we've seen in the previous study -- that there was efficacy protection against serotype 3.

However, we were recently presented with this information which is currently under review that suggests in the Finnish study that there was also evidence of efficacy against serotype 4. Four recipients of the vaccine had serotype 4 and 17 percent of the placebo recipients had serotype 4, giving a relative efficacy of 76 percent which was significant.

There was a mention earlier about the Brazilian study which I believe is 310 -- which shows some efficacy in serotype 2, and we've asked the sponsor to provide us with some more detailed information about that today if possible.

So in summary, we've tried to cover the safety, efficacy, and immunogenicity information provided to the FDA and looking forward to hearing the committee's comments.

CHAIRPERSON FERRIERI: Thank you, Dr. Carbone. We'll open it up for questions from the panel for Dr. Carbone. Dr. Maldonado.

DR. MALDONADO: Yes. I have a question about the placebo recipients who were found to have rotavirus vaccine. In fact, did those children demonstrate seroconversion? Do you have data on that? Or geometric mean titer data?

DR. CARBONE: We don't have that data separated out. I don't know if the sponsor has that data available with them today.

DR. PARADISO: All those children had a concurrent wild infection, so you can't really know. But it was much less of the vaccine virus than the wild virus because the vaccine virus couldn't be cultured. It could only be detected by PCR.

CHAIRPERSON FERRIERI: Other questions from the panel? Dr. Broome.

DR. BROOME: Could you clarify, in your analysis of the cases of just gastroenteritis, etiology not specified, that does include the documented rotaviruses cases of that severity?

DR. CARBONE: All cases -- rotavirus and non-rotavirus. All gastroenteritis as defined by the clinical definition.

CHAIRPERSON FERRIERI: Yes, Dr. Edwards.

DR. EDWARDS: Could you clarify a little bit more about the failure to thrive issue? I know there are some definitions that you can't clarify, but it seems that there is some suggestion, at least from children that were shedding both vaccine and wild type virus, that the vaccine virus in some children might have been shed for a fairly long period of time.

Is there any data on the children that fail to thrive, that they may have been persistently colonized or may have had some gastrointestinal reason so that they would not thrive?

DR. CARBONE: I think there may -- it's a confusing issue. The information provided to us from the 309 and 326 studies were not -- they were not submitted as efficacy data. And we had some

abbreviated information for safety.

When it was reported to us that the vaccine virus could no longer be detected after three months, it was not indicated to us that was a single individual who shed the virus in the three months. It was, were they ever able to recover it from anybody? No, after three months.

So I can't say that that was any evidence we have of persistence. And I definitely don't have the information about the vaccine virus recovery association with failure to thrive. Again, we're currently in discussions with the sponsor to get more information and I don't know if you have that now.

DR. CAMARDO: It's Dr. Camardo again. This is a volume full of basically, very detailed case summaries. What we looked at is what happened to the infants during their developing. We specifically looked to see if it could be related to a chronic gastroenteritis illness and there's just no sign of that.

So I don't think that's the explanation but in fact, all of that data came from the U.S. and Finnish studies, not from the Venezuelan study. But as I said, it's very hard to summarize. It's essentially all these clinical cases which I know

you've asked for and we'll show you. But we did look for a specific cause, you know, some kind of pattern, and we couldn't find one.

CHAIRPERSON FERRIERI: Along the same lines though, did you have growth charts to be able to document where they stood at birth, for example, before they got first dose?

DR. CAMARDO: We didn't require that in the protocol but almost every infant had those. And I think those are part of the summaries -- that information is part of the summaries. But again, we couldn't really detect a pattern. So the best we could do is continue to look for a pattern, and now I think we're going to have the FDA staff help us out.

It took us a very long time to get this; a lot of these were charts in Finnish and you know, we don't see anything that stands out at all after a very meticulous search with the help of the expert.

CHAIRPERSON FERRIERI: Is Dr. Carbone correct that the term "failure to thrive" was used in the American studies, and "growth retardation" in the Finnish study? FTT was American and growth retardation was the term used by the Finns? That would have been my guess, but --

DR. CAMARDO: Yes.

CHAIRPERSON FERRIERI: It's a very broad -- we all know how --

DR. CAMARDO: Yes, it is.

CHAIRPERSON FERRIERI: -- non-specific it is.

DR. ZITO: Ed Zito from Wyeth. Most of the verbatim involved children that were just off the growth curve. They were particularly sensitive to that in Finland, and in the United States likewise. It really seemed to be a weight type of phenomenon.

CHAIRPERSON FERRIERI: Do we have long-term data on those infants to know what they were like one year afterward? After the doses?

DR. ZITO: We have in fact, secured the patient charts for these children as of approximately six or eight months ago. We'll be providing the full package to the FDA.

CHAIRPERSON FERRIERI: Good. There are only 11 charts that would have to be provided. Dr. Carbone, did you want to present something, and then Dr. Snider and Dr. Hall, did you have your hand up?

DR. CARBONE: Just one second. In the request for the specific data, as you can see, the failure to thrive group are many from the 314 study here, and a few from the 316 study. And then if we

look in the growth retarded we see many from the 316 Finnish study here and one from the U.S. study.

So some of the group -- from a clinical point of view, essentially we believe the groups can probably be joined and that the difference in name is purely artifactual. Nonetheless, the cases are of interest to us as they are to the sponsor.

CHAIRPERSON FERRIERI: It looks like a longer list of children than the numbers reflected in your table.

DR. CARBONE: I would remind the committee that the difference was seen statistically only after a subset analysis of children greater than 11 weeks --

CHAIRPERSON FERRIERI: Fine.

DR. CARBONE: -- which was post-hoc. So some of these children may have fallen out in the less than 11 weeks but not found to be statistically significant. So that is also information we are currently engaged in getting from Wyeth.

CHAIRPERSON FERRIERI: Thank you. Laraine, did you have a --

DR. FLEMING: By the way, those are all from the three randomized trails.

CHAIRPERSON FERRIERI: Dr. Snider.

DR. SNIDER: Well, I was going to raise some

points along the same line which had to do with gestational age, you know, birth weight -- height and weight -- you know, their history of growth, as well as subsequent diagnoses --

CHAIRPERSON FERRIERI: Now, those are critical points.

DR. SNIDER: -- you know subsequent diagnoses that may have been made. Thinking along the lines of the subsequent diagnoses I was wondering if any of these children subsequently -- especially those who became ill -- were subsequently diagnosed with some sort of immune disorder, and if there was any relationship with immunologic disorder and shedding of the virus. Is there any information on that?

DR. CARBONE: We don't have any of this additional information beyond the study time --

DR. CAMARDO: Dr. Camardo again. We don't have a lot of specific information on that but we don't have information to suggest that there was an ongoing immunologic disorder or that there was long-term shedding of the virus. We really looked for that and we don't see it.

CHAIRPERSON FERRIERI: Dr. Hall.

DR. HALL: My question has pretty much I think, has been answered here but is again, this

failure to thrive. You have I gather, the knowledge for each child of gestational age, and at the time of enrollment you have the weight of that child at that time.

DR. CAMARDO: We have the weights for every child at every dose. We don't have the gestational age for every child on our database, but we requested that for these children. That might help us to find an answer.

CHAIRPERSON FERRIERI: You sure know what kind of specialties we represent. Dr. Maldonado.

DR. MALDONADO: I want to shift gears for a second and talk about the oral polio vaccine titers. And I know that's not an issue in the United States because we're giving IPV but in fact, eventually if this vaccine is going to be used in developing countries we know that oral polio vaccine does not have the same immunogenicity that it does in the United States.

So I'm not surprised really, that we didn't see a difference in this country, but in fact, the question is whether immunogenicity of OPV might be effective in developing countries when you've got competing viruses of the intestinal tract, and whether or not the Venezuelan study looked at that at all.

I thought that there was some data from Burma, or maybe a few other countries looking at that issue, and I wonder if that data was submitted.

DR. CARBONE: There were some additional data submitted. What we presented was the 10^5 dose. Some of the additional data is at a different dosing schedule or a lower dose of the vaccine. But perhaps if there's some additional information that the sponsor would like to mention?

DR. CAMARDO: We have information on the interference of OPV RotaShield™ from a lower dose, in Thailand.

DR. CARBONE: And what was the result?

DR. CAMARDO: That there is no interference.

CHAIRPERSON FERRIERI: Dr. Modlin.

DR. MODLIN: I think Bonnie's question was an excellent one. I was just going to expand upon that. There have been two studies now -- one done in Bangladesh by Mathu Santosham and his colleagues and another done in Brazil by Peter Patriarca and his colleagues -- that have shown that.

But one of the major reasons why you see reduced immunogenicity for OPV in developing countries -- if not the major reason -- may be rotavirus infection. And there are suggestions that those

infants that are least likely to seroconvert are more likely to have had rotavirus gastroenteritis, and it may be a very strong factor.

So the question of -- answering that question I think, is going to be a critical one for the use of this vaccine in developing countries.

CHAIRPERSON FERRIERI: Point well taken. Dr. Hall, again. Yes.

DR. HALL: Isn't that also though, true John, that with other agents, not just the rotavirus, and that this may be a major cause and was that examined at any point.

DR. MODLIN: Well, actually, yes. I think the point is -- the point of both of these studies was that the rotavirus appeared to -- rotavirus gastroenteritis appeared to be by far, the strongest factor in terms of when an infant had diarrhea during one or any -- at the time of any of the feedings for OPV -- that their chances of seroconverting after three doses of OPV were quite a bit lower.

Granted, there are other causes of reduced immunogenicity for OPV in developing countries, but I think the best information we have at the moment is that not just any gastroenteritis but particularly rotavirus gastroenteritis appears to be the most

important factor.

And maybe Peter or Mathu might want to expand on that. Perhaps, perhaps not. Do I have it right?

CHAIRPERSON FERRIERI: I have a question regarding the co-infection or excretion shall we say, of the vaccine strain and the wild type strain. Were the placebo children within social groups that would have permitted you to assume that transmission of the vaccine strain was likely? I have a hard time understanding this particular point. I may be missing something that Dr. Camardo or one of you -- could you talk to that point?

DR. CAMARDO: It's a very good question, and I'm going to ask Dr. Kapikian to answer it. Al?

CHAIRPERSON FERRIERI: I find it, you know, almost a little beyond coincidence that this should be the case.

DR. CAMARDO: In fact, you're really looking at an isolated study -- not isolated, but one of the studies of transmission. There are some other studies and you may want to see those if we have the time. But it's really Al's question to answer.

DR. KAPIKIAN: As you know, the virus is shed in the stool regularly by probably 80 to 90

percent of the individuals who receive the vaccine strain.

And in addition to that, in this population in Caracas the children were very crowded together and we did not anticipate this, as you suggested. We did not anticipate this happening and it had not been described previously.

But when we received these 213 specimens from Caracas which had been obtained from children who were ill already and Dr. Perez-Shell sent us these specimens for serotyping purposes, and we serotyped about 48 percent of the specimens using an ELISA test using monoclonal antibodies for each of the four serotypes.

Because of the fact that there were other serotypes circulating in Latin America, for example serotype 5, before we broke the code we felt we ought to really try to serotype more than 48 percent of the specimens, where most of them were serotype 1 when we did our typing with ELISA reagents.

When doing that with Dr. Hoshino -- who's here in the audience -- by PCR and using other methods, we found that we could serotype all 213 specimens. They were all serotyped.

And again, most of them were serotype 1, but

in 29 instances we found, in addition to serotype 1 and a few serotypes 2s and one serotype 3, we found that there were 29 specimens that were serotype 3 or one that was serotype 4.

So because of this, we then wondered, what was this other virus that was present with a wild type virus? And this took us about six months to sort this out. We started out with a sheet this wide; we wound up with a sheet this wide because of all the tests that had to be done to establish this was indeed, not a laboratory problem.

And what we found was -- by the PCR method VP7, that most of these other viruses were serotype 3 as I said, but then by doing VP4 analysis by PCR, found that these were Rhesus rotavirus VP4 and not 1A which is the wild type serotype for the p. Now, it gets a little complicated but p has its own serotyping system.

With that finding we then said, well this is a vaccine strain that is being shed by 29 of these individuals. Now, we have not yet broken the code at this time, but in order to really nail this down one of the things that we wanted to do in addition to doing electrophoresis and doing tissue culture growth, Dr. Hoshino took every stool specimen in the study --

the 213 of them that were from ill children that were already positive for wild type virus -- and inoculated a ten percent suspension as Kathryn said before, into six well plates and it determined what was being shed.

And at this time we were able to confirm in most instances, that as you picked the plaques that these viruses that were being shed were indeed, Rhesus rotavirus-like -- of the 29, 28 were Rhesus rotavirus; one was ST3 times Rhesus rotavirus -- and among the Rhesus rotavirus, four of them were Rhesus plus ST3 times RRV.

There was no question in our minds that then this had been confirmed by doing these various assays because we had to be certain it was not a PCR contamination; that we were then certain that it wasn't.

But the study -- it was a very anxious moment because there were two possibilities. Was this then, a persistent virus that maybe all 29 were in the vaccine group and we did not know? And so we went to Caracas to break the code.

When the code broke we found that the distribution of the vaccine in the stool was 13 percent of the placebo group and 15 percent of the vaccinees had shed this virus. So we knew that this

wasn't just for the -- it wasn't persistence in the vaccinated individuals. The placebo individuals also had a vaccine strain in their stool with a wild type virus in addition to their vaccine.

The other question really is a very important one then, that we felt at that time could have really been very detrimental to the study, was the fact that individuals were shedding two viruses at the time. Did that make the illnesses more severe? And obviously if it did again, it would have been really a great detriment to this vaccine.

When the code was broken, 29 individuals had dehydration in the study and they were the most severely ill people in the Caracas study -- 29. And of the 29 who were dehydrated as the code was broken, five of the 29 shed wild type virus plus the vaccine strain, and 24 shed only the wild type virus.

So again, there was no indication that shedding the vaccine strain plus a wild type had potentiated the disease. So what we're really trying now to do would be to, we're looking at some other studies -- we're looking at the American Indian study for the same reason.

We've received all the specimens from Dr. Santosham's lab -- about 350 of those individuals who

again, this in a sense is the numerator study in that there are only children who are ill and are shedding rotavirus.

We've also received specimens from Dr. Linhares from Brazil to look at the same question. We've also received selected specimens from Dr. Vesikari in his study, and we are looking at that. But I think ideally what we are planning to do will be more of a numerator-type study where we take individuals who did not have rotavirus and try to examine what the rate was of this phenomenon occurring.

One other final point I'll make is that, when we had submitted our paper to The New England Journal of Medicine on the Caracas study, several reviewers had stressed that we had underplayed the fact that there was this vaccine virus being shed and they said, this was a rather beneficial event.

That what you did was, in a way you might have underestimated your efficacy because of the fact that you in a sense now, had vaccinated the placebo group perhaps, and that you may have heard in unity and so on. And they went into this in great detail.

But it was my strong feeling that we should be very conservative about this point; that we really

hadn't established this. And so in the paper we just put a little sentence about this to satisfy the reviewer because the analogy was being drawn for polio vaccine; that this might do the similar effect as the polio vaccine did.

So I think the question is still, when I see those second years when there's no rotavirus around when I see those charts, I sometimes wonder maybe the vaccine has done some spreading.

But again, that's all anecdotal, we don't know that, and I think it's going to determine some really interesting epidemiologic data looking at denominators in addition to the numerator. Because we're now in a numerator study; we should get a denominator effect, too. So I don't know if that answers your question or not.

CHAIRPERSON FERRIERI: While you're still at the microphone, I have a question that reveals my simplicity on the biology of rotavirus. But if you mix in a test tube or in cell culture, the wild strain with a vaccine strain, do you have any evidence of any exchange of genetic material?

DR. KAPIKIAN: Well, various people who have done that, there is reassortment in cell culture; reassortment in cell culture does occur. The thing

that we try to do to extend it -- but this is still developmental -- those children who have shed the wild type virus and are also shedding the Rhesus virus, we looked to see if there was reassortment in those individuals.

And Dr. Hoshino and Ms. Watson who's here also, looked at this by hybridization and so far have not found this to occur. But it doesn't mean it doesn't occur. I would be surprised if it did not occur; it probably will occur, and it would not be a surprise and it wouldn't be a detriment to the vaccine either.

So if we look we're going to find it just as it occurs in nature. Wild type viruses do reassort and why wouldn't the Rhesus rotavirus? We know there is data that the feline rotavirus and human viruses -- there are VP4 for feline in a study done in Japan and also there is bovine data similar.

So I wouldn't be surprised if that occurred.

CHAIRPERSON FERRIERI: Thank you so much, Dr. Kapikian. Dr. Karzon.

DR. KARZON: Dr. Kapikian prompts me to bring up some side issues, and you may comment on them, but I'd like some general comment to it or perhaps I'm over-concerned about some things.

I think the lack of an easy way to identify protection, commonly called the correlates of protection, may haunt us for a long time with this virus. I don't know how much we know about that now. I don't know how difficult it would be to come by such information.

We have three proteins that are -- I understand are antigenic -- so we have three antigen antibody systems. We are looking in particular about protein 7 and its consequences in group A strains, but there are many other strains we will encounter in the world certainly, if not in the United States.

The handicap here is that we don't have a marker -- even a surrogate marker -- of protection. And that will handicap lots of things in real life administration of the vaccine.

The basis of giving three doses of vaccine I haven't heard. There's probably some information about takes in the gut, titers, resistance, and effect on some elements of immunity. Why are three doses necessary and what is the effect?

And again, in real life we're going to be immunizing children let us say, at two, four, and six months, for convenience. We don't know in given populations whether two months is a correct point in

any passive antibody that it's offered protection till that time.

I'm not clear on passive antibody and whether that's looked at and whether we should give it earlier or later; what happens if we skip a dose; what happens if we wish to immunize children at six years for various reasons; what happens in three different populations that have been defined in terms of this virus?

There's one population demonstrated by the American indigenous population where there's very rapid, early transmission of virus. Now, to prevent that virus we have to be on the early side. Apparently, maternal antibody -- I don't know the stated internal antibody -- doesn't protect these infants very long, because they get clinical infections.

And then the general population of the United States if there is such a thing -- so called lower socio-economic groups in the population, those that don't have a telephone -- and countries like Finland that we know from other epidemiological studies, may delay passage of agents.

Hib was interesting in terms of late appearance and late pathology in the Finnish

population. So do they have to be handled differently?

What about when a child is born and when he's two months of age when he gets the first dose, in relationship to the winter season. So he's entering the winter risk season at different ages.

Another big issue which has been mentioned but only in a one-side thing. We know that polio -- and we'll probably look at measle, mumps, and DTP in more detail -- we want to make sure that giving simultaneously or even combined vaccines will affect those agents.

But how will we know whether it affects the efficacy of rotavirus when our tests for rotavirus efficacy are clinical trials to show that there's alteration in the protection rate in that population? We don't have quick, handy things that we could look at like Hib. We know a threshold tie to polio.

We know a titer and we can see whether there's suppression. We won't be able to see what's happening; it's a black box.

IgA has been mentioned as a surrogate -- serum IgA. And I think that's a very weak position to take. We really don't know the congruence of IgA -- with secretory IgA which we really want to know. We

don't know what the CTL response is in the gut and I think that's a morass I wouldn't suggest exploring. But we could look at the secretory IgA.

I'm sorry for the time, but I think these things are going to bother us in the future and it seems to me be worth looking at methods to try to get some correlates of immunity.

CHAIRPERSON FERRIERI: Well, those are all good points. Dr. Kapikian, you may wish to --

DR. KAPIKIAN: I think --

CHAIRPERSON FERRIERI: -- address the major question to start with; with the three doses for example. Some of the others may not have an answer right now.

DR. KAPIKIAN: David, that's right. If I began to give our strong feelings about protective immunity, there are many opinions in this room by various people and we differ markedly on what are the parameters of protective immunity.

But to answer your last question first, the value of doing an IgA test is, that since the IgA does not cross the placenta and we're going to obtain the blood, frequently at one-and-a-half months of age before the first dose, we don't confound the results by having a high level of antibody in the pre-

vaccination serum.

So we use the IgA ELISA test for that reason and this has worked out very well, as I have said frequently in other forums. The main thing we want to be sure of when we do the IgA test is that we're not giving water, we're giving something that is immunogenic.

And when we established the dose of 10^5 as was used in all these studies, with Dr. Flores and Irene Perez-Shell in Caracas, we did 12 studies to establish the fact that we needed two doses. We actually started at a quarter-dose of what you see here, a half-a-dose, a full dose, and then we increased it from 1 X 10^4 to 1 X 10^5. We even looked at 1 X 10^6 of individual serotypes -- type 1, 2, 3 or 4.

In 12 studies it took us about 18 months to do to establish the proper dose. And there, we did neutralization tests to try to achieve a level of 50 percent take rates by each of the serotypes: 1 X 10^6 was not substantially better than 1 X 10^5, and 1 X 10^5 was better than 1 X 10^4, which was much -- and so on. And others have done other titrations.

So we didn't just pick this dose out of the hat. We did 12 separate, phase 1 studies over a year-

and-a-half with Dr. Flores.

Well, the question of 3-dose is an interesting one. This was really in a sense, put upon us by various organizations in that they said, two, four, six months of age at that time was oral polio; that was being given at two, four, six months of age.

And they said, do it during the time when they're going to be given the oral polio vaccine. You can give this vaccine orally simultaneously -- the WHO, they had that feeling and they had it also in the review committee for the Caracas study.

We actually thought two doses might be sufficient but we went along with the 3-dose. So that's really how that happened. And maybe variations later on will be arrived at in further studies. But the parameters of protection are an interesting question.

However, when I see the data like Dr. Santosham's data that there is serotype-specific protection by the tetravalent vaccine and not by the monovalent vaccine against serotype 3, I get very encouraged that our approach is a valid one.

And also when I listen, when I see the other studies -- Peggy Rennels' study and the one that Bernstein did also, the multicenter studies -- where

there was a strong trend for serotype-specific protection, I think we're not really barking up the wrong tree.

I think protective immunity is there and I think that antibody does count and that serotypes are encouraging to us and there I can pick data that support what we're saying and others in the room will pick data that don't support it, but -- as far as what are the parameters of protection.

But I think that -- I hope that answers at least some of the questions.

CHAIRPERSON FERRIERI: Thank you, Dr. Kapikian. Dr. --

DR. FLEMING: Just to enter a brief comment, though. Your closing comment was, protective immunity is there. My sense was, that's not the question though. The overall, global data are suggesting protective immunity is there. The fundamental question is by what mechanism, so that we can in fact, use a correlate as a potential surrogate.

DR. KAPIKIAN: Yes, but we have -- but the vaccine when it was compared as a tetravalent vaccine against a monovalent vaccine, the tetravalent vaccine has four of the immunogens in it; the monovalent had one.

Protection was certainly significantly better with the one that contained immunogen for type 3 better than the one that did not have it in. So that's circumstantial evidence but it certainly does support this concept that specific antibody against individual serotypes was necessary to yield protection.

Now, if you want to get a certain level of antibody and you want all of that, I can cite studies where that was shown, but others could cite others where it wasn't shown. So I don't want to get into that.

DR. FLEMING: That's the issue.

CHAIRPERSON FERRIERI: There will be one more question before the open public hearing. Dr. Estes.

DR. ESTES: I'd just like to make a comment about this point of protective immunity. There's been increasing evidence in animal models and there are a few studies in human -- in children suggesting that intestinal antibody, whether it's IgA or IgG, may be a useful, correlative protection.

And I am actually a little surprised that there have not been any studies in relationship to the vaccine where this has been looked at directly.

Because it's very clear from the animal studies that I think those correlates are quite strong.

CHAIRPERSON FERRIERI: Thank you.

DR. KARZON: I want to make something clear to my old friend. I would have thought the same thing with the lack of other information. I think this was beautifully engineered and carved out. So Albert, I couldn't critique anything but -- characterize it as beautiful, the work that's done. And I'm not talking about that; I'm talking about the future.

CHAIRPERSON FERRIERI: Thank you. Dr. Goldenthal, has FDA seen the data that Dr. Kapikian presented that is in vitro, sorting out, using various assays, vaccine strains versus wild type? I assume you have not, and I'd like to suggest that if you haven't that that data be scrutinized. No lack of confidence, but I think that if you're looking at everything else you might as well look at that as well.

DR. CARBONE: You're referring to the immunological --

CHAIRPERSON FERRIERI: Yes.

DR. CARBONE: Yes, we're actually --

CHAIRPERSON FERRIERI: The strain characterization, the verification of the

differentiation of wild versus vaccine strain.

DR. CARBONE: We were actually -- yes, we actually received a tremendous amount of detailed information about antibody responses, neutralizing test to each of the strains, and with many of the studies a tremendous amount of data were collected.

The bottom line though was, when it was all compared against the efficacy and who got the vaccine and who didn't and who was protected and who didn't, not one of those markers could be directly associated with protection from rotaviral gastroenteritis.

Now, there was some question and I might want to ask Wyeth to comment about studies done with stool antibodies. I don't know if you have any additional information.

CHAIRPERSON FERRIERI: I'm speaking just of the Venezuelan study, Dr. Carbone, and the strain differentiation.

DR. CARBONE: In the stool study?

CHAIRPERSON FERRIERI: In the stools, right; placebo versus vaccinees.

DR. CARBONE: Right, right. We can always use as much information as they can supply, on that -- on those studies.

CHAIRPERSON FERRIERI: Did you have a

response to her other point?

DR. CAMARDO: There's a little bit of data suggesting that there is gastrointestinal IgA but it's just very small. And I think one of our problems was that when these trials were being run, the earlier ones -- '91, '90, '89 -- there wasn't really a great method for getting this in a large-scale trial. And if the techniques have improved that might be able to be done in the future. But it just wasn't really feasible to do that an easy way.

CHAIRPERSON FERRIERI: Dr. Hardegree. And then we will do the open public meeting.

DR. HARDEGREE: One of the things that was discussed at the ACIP but I don't think has been discussed here, was some data and information about intussusception. I think it relates to the safety issue. And I wonder if Dr. Rennels would comment on that point.

CHAIRPERSON FERRIERI: Does it require a slide, Dr. Rennels, or can it be summarized?

DR. RENNELS: Well, it can be summarized. When I independently was reviewing hospitalizations for gastroenteritis the seven days post-vaccination, I came across one child who had received vaccine who had intussusception. So I then reviewed the entire

integrated safety summary that was sent to the FDA to look at all cases of intussusception.

And I found five cases of intussusception among placebo recipients. Now, that is different vaccines, that is three different doses, two different formulations, two different buffering methods. And I didn't find any among the placebo recipients.

These cases of intussusception occurred following dose 2 or 3 and they followed, oh, they were six to 51 days after vaccination. Now there were no significant differences in the rates of intussusception between the vaccinees and controls, but I was -- by either Fisher's or Poisson -- but I was concerned that with larger numbers perhaps a causal relationship might emerge.

And I looked in the literature -- can I take five minutes here or do you want it not so thorough?

CHAIRPERSON FERRIERI: It won't be that easy -- a minute or two maximum I'm afraid, Dr. Rennels.

DR. RENNELS: Okay, there's no help in the literature. The literature, out of two out of three studies, uncontrolled showed no association. With the help of people from the FDA then we looked whether intussusception itself had a seasonality -- and it doesn't -- compared to rotavirus.

We thought this was a strong argument against wild rotavirus-causing intussusception. We also looked at the ages of intussusception to see if it was skewed by vaccination. Intussusception in background population peaks between about four to nine months which is exactly when we saw it; it was not skewed to first dose.

And then we compared different background rates of intussusception to intussusception among the vaccinees and broke it down. I was able to compare Northern California by these age groups and all rotavirus vaccinees -- RotaShield™ vaccinees, and found that there were no significant differences.

I was able to find other background populations to compare less than 12 months of age. And again, if you compare all of these other background populations with the RotaShield™ vaccinees, there were no significant differences and in fact, RotaShield™ vaccinees, the rate per 1,000 of intussusception was lower.

So I included the intussusception was probably due to chance temporal association.

CHAIRPERSON FERRIERI: Thank you. We have an announcement now, prior to the open public hearing, and as we move forward we need to keep on schedule or

we will not have a panel left, we will not be voting on the issues. The meeting will come to a close without any resolution.

MS. CHERRY: I'd like to move right into the open public hearing session. At this time members of the audience are given the opportunity if they wish, to make a statement. Is there anyone that wishes to make a statement?

CHAIRPERSON FERRIERI: Dr. Halsey.

MS. CHERRY: Dr. Halsey will speak.

CHAIRPERSON FERRIERI: And the rules of the game Nancy, are what?

MS. CHERRY: He will now speak during open public hearing. I'm afraid he was excluded from the meeting.

CHAIRPERSON FERRIERI: And so the rules are that he can speak but cannot ask questions of people who have spoken? Is that what it is?

MS. CHERRY: That's true.

CHAIRPERSON FERRIERI: And so this may seem unnecessarily cruel but these are the FDA rules, Neal. And I'm told also that what you say is independent of the rest of the meeting.

DR. HALSEY: Thank you for the opportunity to speak.

(Laughter.)

Briefly, I can't vote and sit at the table because of conflicts that faculty who work underneath me -- just for the rest of the public to know that -- who do have more significant conflicts.

I'm going to speak on behalf of the American Academy of Pediatrics and as Chair of the Committee on Infectious Diseases who will be writing guidelines for the use of this vaccine.

And I only make it a plea in an effort to try to avoid additional, potential conflict between the package labeling and the guidelines that would come out, that at least have permissive language with regard to the upper age cutoff for the use of this vaccine. I think it will create confusion and difficulty if there's a stringent rule saying you cannot administer the vaccine beyond 30 weeks of age.

As I think most people appreciate, children do not all get immunized exactly at two, four, and six months of age. If we have a recommendation to give this vaccine at two, four, and six months of age, unfortunately many children fall behind the schedule and that third dose will not be given prior to exactly the end of six months of age.

And we need to have flexibility in terms of

administering that. From everything I've seen here today I don't see any reason that those children should not be allowed to complete the immunization schedule, and we do have a substantial burden of disease beyond six months of age, as was pointed out by Roger Glass.

Thank you.

CHAIRPERSON FERRIERI: Thank you very much, Dr. Halsey. A member of our committee was also excluded today. Dr. Clements-Mann, do you have anything that you wanted to say during open public hearing?

DR. CLEMENTS-MANN: I just want to say that it's not for lack of looking for correlates of immunity, but I would like to clarify something, that in human populations it's been exceedingly difficult to acquire meaningful data from intestinal IgA without actually doing intubation and getting upper GI-type fluid, because there's a rapid degradation in the stool of the IgA.

I know that, particularly working with other vaccines where the University of Alabama group has been working very hard with us, we have not yet solved the problem with how to get meaningful data from intestinal IgA measurements.

And if anyone has any ideas about that I'd particularly be interested in learning about that. Thank you.

CHAIRPERSON FERRIERI: Thank you, Mary Lou. Other members of the audience? Dr. Santosham, would you like to make any comments? I saw you in the audience.

DR. SANTOSHAM: Thank you for the opportunity. One question that's often been raised with me because I've done a lot of work on oral rehydration, is do you really need a rotavirus vaccine? Because all you need to do is treat them with oral rehydration. Why both with the vaccine?

Having worked on oral rehydration for over 15 years and trying to push that concept in this country, I think we have had some degree of success as you see from Roger's data. The deaths have come down but then in the last seven to ten years they've plateaued out. And educating physicians is much more expensive than giving immunizations.

(Laughter.)

And the same is true in developing countries. They came down -- after the introduction of oral rehydration in the '70s it came down very rapidly and then it plateaued out. So I don't think

oral rehydration is a reason for not licensing rotavirus vaccine. There may be other reasons, but not oral rehydration.

Just one other comment about the population that I studied and just talk about how similar the data are between the Native American trial and the multicenter trial. We've always been criticized when we do trails; people say, it doesn't really represent the U.S.

I think to some extent that's true. We in a way represent both developing countries and the general U.S. population; people always talk about -- the same came up in the Hib trials. If the vaccine works in the American Indians will it necessarily work in the general U.S. population?

Here we are very fortunate that we actually have shown -- we have good data in a diverse population. So I feel very good about the efficacy data. Thank you for the opportunity.

CHAIRPERSON FERRIERI: Thank you, Dr. Santosham. Any other member of the audience that would like to speak? If not, I'll return to the panel and prior to starting the questions that will be posed by Laraine Henchal -- you would be posing the questions again to remind us -- are there any other

unresolved little questions? Yes, Dr. Snider.

DR. SNIDER: This will relate to one of the questions I think we're being asked, and I just need to be reminded of what information we have about safety -- particularly fever in older children -- as relates to the issue that Neal was bringing up.

I think there was a chart that was shown but I don't recall the ages of the children. As I recall, fever went up and then started to go back down again. But do we have data on fever in children who were immunized beyond six months?

DR. CAMARDO: We allowed the third dose to be completed up to 32 weeks; that's eight months. So the end of that tail cohort that you saw -- which if you want we can show you again -- are the later, you know, are the children in the six months to eight months range.

As I said, the investigators and parent were very compliant. We called them, we did everything possible. But I don't think the 6-month cutoff should be considered as rigid. In fact, there were -- you know, a lot of children went beyond that.

DR. SNIDER: Is my recollection correct that it went up and sort of peaked around four months and starting coming back --

DR. CAMARDO: Yes, that's correct.

CHAIRPERSON FERRIERI: One last question. Dr. Estes.

DR. ESTES: I had a question. As I understand it, pre-term children were not excluded from immunization, but I didn't hear if any pre-term children were actually immunized.

DR. CAMARDO: Yes, about 70 pre-term children were immunized. For -- well, about 60 to 70, Michael, is that about right? All right, 36 and 34 in the RotaShield™ placebo groups. Now unfortunately, we only have the actual gestational age for about 20 of these infants. The rest were noted to be premature but we don't know how premature they were.

I guess I'm showing a slide. I did say, you play it and I'll sing it, but what we're showing here is RotaShield™ in that sort of orange-ish color and the placebo in blue. And what you see is the number of infants in each group -- 36 weeks at birth, 35, 34, 33, 32, 31 -- you see it's not a lot.

And then this group of unknown. The unknown represents infants who we know are premature because the casebook said they were premature. We don't know the age, okay. Because we didn't specifically ask for this data; it's passively collected.

Now, what I can show you is a couple of different things and what we were interested in -- I'm showing you the reactogenicity, post-dose 1 for the infants whose gestational age we know. And these are the RotaShield™ infants. This one was born at 30 weeks, received dose 1 at 17 weeks of age, had diarrhea, vomiting, and another infant who had a fever.

The next slide shows that there is reactogenicity in the placebo preemies as well -- fever and diarrhea. The point is, we're not seeing anything unusual, long-lasting, serious illness here.

And if you look -- I'm not going to show you this, but if you look at the rate of fever, diarrhea, vomiting side effects in the placebo versus RotaShield™ groups for all the, about 70 infants who were premature, there's actually no reactogenicity, and the incidence compares pretty well with the non-premature infants.

So it's a small amount of data; wasn't randomized. But it turns out that they were, you know, half in each group. But we don't see anything serious in the small sample that we do have.

I mean, we're inclined -- as Dr. Halsey said about permissiveness in the older age group -- we're

somewhat inclined about permissiveness here, as long as the infants were healthy at the time that they're required to get the first dose.

CHAIRPERSON FERRIERI: Thank you. Slide off; lights, please. There's one question, Dr. Hall, and then we are starting the questions now.

DR. HALL: The question with the fever I think, is not so much whether there's a third dose given after six months, but if we have any information about what may happen in the real world of the first dose which is associated with fever, being given after six months. The reason being that febrile seizures, which is really what one may be concerned about, do not occur until six months of age.

CHAIRPERSON FERRIERI: Any response to that, briefly?

DR. CAMARDO: We don't have any data from this dataset in infants receiving the first dose after six months. We have some adult studies, and Peggy, could you comment on it? I mean, there's a little data but there's nothing in the dataset I showed you.

DR. HALL: I'm talking about Native --

DR. CAMARDO: No, exactly right. We have no data from the dataset.

DR. RENNELS: Back when I didn't have gray

hair, before Wyeth ever acquired the Rhesus rotavirus vaccine, with Dr. Kapikian I did some first study in children in which children were enrolled between, I think it was three months of age and 20 months of age.

And I was able to show that children over five months of age had a higher frequency of fever. And in Venezuela that was shown also, and then with a different rotavirus vaccine Canada it's been tested by a different company, they found the same thing.

CHAIRPERSON FERRIERI: We're back to the heart of the meeting now, and the end of the meeting: the voting questions. Dr. Laraine Henchal.

DR. HENCHAL: Okay, these are the voting questions. The first one is: Do the data demonstrate the safety of RotaShield™? The second one is: Do the data demonstrate the overall efficacy of RotaShield™ for immunization of the proposed target population?

Number 3 is: Do the data support greater vaccine efficacy against severe rotavirus gastroenteritis? Do the data demonstrate vaccine efficacy during a child's exposure to a second rotavirus season? And lastly, do the data support co-administration of RotaShield™ with other routine childhood vaccines given at two, four, and six months

of age? For example, OPV, DTP, and Hib.

Then in addition we have some discussion points that we'd like comment from the committee on any that they think merit further discussion, especially with regard to post marketing studies; and for number 5 specifically, the issue that Dr. Halsey has brought up about the labeling for the restriction about the dosing between six and 30 weeks and what will we do about children who are older who have initiated the vaccine series and then are older than 30 weeks when they need their second or third doses.

So these issues are: the issue of RotaShield™ with other childhood vaccines that are currently being administered for which we have not yet available data -- such as Hepatitis B, the DT acellular Pertussis and the IPV; efficacy against the rotavirus serotypes which are not prevalent in the U.S.; safety for vaccination of children in contact with compromised hosts.

The safety and efficacy when used in infants born prematurely -- of course, we just saw that information so maybe we don't need to discuss that further. Again, the safety in the older children; and efficacy when administered to breastfed infants.

CHAIRPERSON FERRIERI: Thank you, Laraine.

We'll start systematically and go down one question at a time.

Do the data demonstrate safety of RotaShield™? I'd like to use a format where I'll call on a few people, others can spontaneously -- on the panel only -- add to the information, and then we will go around and all the voting members will officially vote.

I'd like to start with Dr. Fleming. What do you think, Tom, on the safety of RotaShield™?

DR. FLEMING: Thanks, Patricia. One question that I had asked just before the break that is, certainly for me at least, relevant in answering this question related to -- and it looks like you're holding up a transparency. Can you flash it up there?

My question related to the specifics for a hospitalization due to RVGE, which is an efficacy measure, and then due to febrile illness as a safety.

DR. KOHBERGER: Data randomization, Tom.

DR. FLEMING: All right. Okay, quickly can you just quickly summarize what you have there for us?

DR. KOHBERGER: This is all hospitalizations; this is the number of episodes; number of subjects. This is for GI. This is what we could get you. In addition, if you would like two

weeks post the last dose, RVGE is zero, 1, 5, 6, and zero/13. We couldn't get from the data randomization for RVGE.

CHAIRPERSON FERRIERI: Thank you.

DR. FLEMING: And when you have GI down there -- 316 for example -- 18 versus 29, those include the previously referred-to zero versus 13?

DR. KOHBERGER: Yes, zero versus 13 is included --

DR. FLEMING: Are included in there, okay. And then the seven versus two febrile illness, do those show up in the bottom or only in the top?

DR. KOHBERGER: I don't know where the febrile illness -- they would certainly be in all, but it depends on whether or not the diagnosis for febrile illness is here in the GE. I don't know that right now.

DR. FLEMING: Okay, let me just press ahead then, with the best answer that I can subject to what information that at least I see we have.

In my view, the issue of safety is relative -- in my view, has to be put in the context of efficacy as well. With what we are looking at here globally is, safety information that shows that, relative to other childhood vaccines, my sense is that

this safety profile is in the range of what we would see elsewhere.

The issue that I try to weigh out though is, against what level of benefit? And specifically, if we're seeing for example, febrile hospitalizations on the level of a half to one percent, and the essence of what we're trying to achieve from an efficacy perspective is prevention of hospitalizations for example, on the order of a half to one percent, then that safety consideration would be viewed differently in my mind, than if it were in a polio setting where we're trying to eliminate a condition that would be more of it in long term, or substantially, would involve mortality.

Roger Glass had made a comment that I wrote down almost verbatim, as he had been talking about the U.S. setting and his epidemiological assessment, then went on to developing countries. He said, a prime target besides the U.S. is developing countries.

And I think he would acknowledge that's an understatement given the fact that when we're looking at this worldwide these refer to a million deaths worldwide and 20 to 40 per year in the U.S.

And so if we put safety into context within the U.S., my sense is that the intervention is, in

fact, that vaccine is relatively safe and yet the level of serious side effects -- for example, when we look within the Finnish trial when there is a rate of a half-a-percent higher hospitalization for fever above 39, and when we see fever levels above 38 of 30 percent versus 49 percent, globally congenital anomalies, growth retardation, failure to thrive in the excess of a half-a-percent.

And then on the less serious level -- but meaningful level -- appetites, irritability, activities increased by six or seven percent. My sense is that clinically we will look at this as being not substantial safety concerns but when we come to question 2 I'll try to put it in the context with exactly the level of clinical benefit that we're achieving and I'll re-ask the question: as we look at level of efficacy, how much of a safety risk is acceptable?

CHAIRPERSON FERRIERI: Dr. Broome, do you wish to add to this issue, your impression from the data, of safety?

DR. BROOME: I guess I just would ask Tom to clarify whether we have any information about hospitalizations for febrile. The Finnish paper didn't --

DR. FLEMING: The table that's near the end that I think Dr. Camardo had presented, referred to -- and this is I think, page 41 at the bottom in his handout, Claire -- had referred to seven hospitalizations for febrile illness on RotaShield™ and two on placebo.

Which is about half-a-percent increase which is being weighed against slightly more than a one percent decrease that the RotaShield™ provided in hospitalizations for RVGE. And it's in that sense that I'm thinking that --

DR. BROOME: No, I think --

DR. FLEMING: -- that there's some relevance to it, when you look at it in that sense.

DR. BROOME: I think it's a very reasonable context and that's what I was trying to get a sense of: what's the overall impact on gastroenteritis hospitalizations? Is there any evidence of replacement disease, which it looks like overall, there is an impact on total gastroenteritis, not just that related to rotavirus.

My sense is that the safety issue of major concern are the febrile episodes. I'm not totally sure what to make of the failure to thrive, growth retardation differential. And I think Karen's point

about what's the febrile rate in children receiving a first dose over six months is a particularly valid one in that context.

I'm not sure we're going to have any -- we don't have any data to address that but I think -- you know, the febrile reactions are a little higher than I'd like to see, but I don't think they're completely out of line with other childhood vaccines.

CHAIRPERSON FERRIERI: Dr. DuPont, do you think the data presented are adequate for us to assess the safety of the rotavirus vaccine?

DR. DuPONT: I do. I think it's hard to separate the considerations of safety from considerations of efficacy, but I think that the side effects, the reactogenicity of the vaccine is probably acceptable and within range of other vaccines that are currently being used.

CHAIRPERSON FERRIERI: Other member of the voting panel?

DR. EDWARDS: I would like just a little clinical comment about the severity of these two illnesses. And I think that for someone who does vaccine trials in young children, if you get a high fever one does have some level of anxiety. Obviously, these are placebo-controlled trials.

Would Peggy have any comment about the severity of these illnesses or would these children like, rule out septic episodes or were they really not so severe in their episodes?

CHAIRPERSON FERRIERI: Dr. Rennels.

DR. RENNELS: Well, I didn't -- neither of those cases occurred at my site, so I don't have firsthand experience. And one of the cases I -- I believe one of those cases I have the entire chart and I would say that that child, you know, had moderate fever and was moderately -- had moderate gastroenteritis.

The second child however, had -- now this is recollection -- rather low-grade fever, mild gastroenteritis that didn't even fit the definition. And you know, just looking at the paperwork it was questionable why that child got admitted.

Now, at the time we started this study -- this is the first time we were doing it at this dose -- and as soon as there had been one or two hospitalizations a letter was sent to all the investigators that had us all, you know, really hyper-vigilant on these children. That's the best I can tell you.

CHAIRPERSON FERRIERI: Is Dr. Santosham

considered part of your expert witnesses who are here?

DR. CAMARDO: I didn't know we were on trial, but yes.

(Laughter.)

CHAIRPERSON FERRIERI: You'd better believe you're on trial.

(Laughter.)

Dr. Santosham, I apologize if I didn't recognize you immediately but he's validating you.

DR. SANTOSHAM: Thank you. I just wanted to comment that I reviewed every one of the fevers in our study. They were all mild illness and self-limited. We didn't have any serious illnesses.

CHAIRPERSON FERRIERI: Thank you. Does the panel feel ready to vote on this? Okay, Dr. Snider, we're voting yes or no: Data demonstrates safety.

DR. SNIDER: My answer is yes with the caveat that we look at -- that the failure to thrive issue be looked at and FDA and the sponsor feel comfortable that nothing severe has happened to those particular children.

And the other caveat of course I'd say, the answer is yes for those of the ages at which the vaccine was administered. And we don't know about the older age groups and I think you know, the issue that

Caroline and I were trying to get at is still not answered.

CHAIRPERSON FERRIERI: Dr. Edwards.

DR. EDWARDS: I would concur. I would suggest that there be continued attention to the issues regarding hospitalization, particularly for febrile illness, if and when this vaccine is licensed. Because I think that also continues to be somewhat of a question for me.

CHAIRPERSON FERRIERI: Dr. Hall.

DR. HALL: I would concur, particularly with what Dixie has said with those two caveats. We would also like to mention that with the febrile reaction that maybe this will need to be considered not only in terms of hospitalizations but in terms of outpatient visits also.

CHAIRPERSON FERRIERI: Continued to be monitored post-licensure?

DR. HALL: Right.

CHAIRPERSON FERRIERI: Dr. Fleming.

DR. FLEMING: I think I have similar caveats as I've indicated earlier. My sense is that the safety profile is within the range of what we would see with certain other childhood vaccines, but in my belief what we should tolerate here has to be

influenced by what the level of benefit is that we are anticipating or that we are demonstrating.

And as a result, I would ask the FDA to work with the sponsor to further quantitate what these serious side effects are -- specifically the adverse effects, driven in particular by febrile illness -- is inducing hospitalizations and what is that level of access. I still don't feel like I have a good grasp of that at this point.

And then the less serious complications -- such as appetite, irritability, and activity -- are we assessing those to be at a level less than essentially what we are gaining in prevention of the severe RVGE.

CHAIRPERSON FERRIERI: Dr. Estes.

DR. ESTES: I would say yes but I share the same concerns that you've heard from the other panel members. I don't need to add more.

CHAIRPERSON FERRIERI: Thank you. Ms. Cole.

MS. COLE: My answer is yes and I feel the same way; that we should just be very careful.

CHAIRPERSON FERRIERI: Thank you. Dr. Broome.

DR. BROOME: Yes, with the same

CHAIRPERSON FERRIERI: Dr. Karzon.

DR. KARZON: I say yes, but I would like to

see actual data on the syndrome that the infant had that caused hospitalization, and question whether that child would have been hospitalized in the United States, especially in the current climate of care.

If we have an FUO in a small child, that gets attention of the pediatrician, but it may or may not end up in the hospital. It may or may not end up in his office, even. So we should document that, and it's documentable, perhaps with great effort and translation.

The second point that was mentioned is this failure to thrive. This is terribly important if it's real. And again, we should be able to get that data. And I feel more comfortable if the latter turns out to be happenstance -- nothing to do with anything, which is possible -- and whether the hospitalization was prompted in part, because of the Finnish medical system, in part because it was a trial and everybody was worried.

CHAIRPERSON FERRIERI: Thank you. Dr. DuPont.

DR. DuPONT: Yes.

CHAIRPERSON FERRIERI: For the record, my vote is yes, but echoing the concerns indicated. Everyone, I think FDA needs to really register the

level of concern of the panel members and the need for obtaining the data that we've asked for, for scrutiny. We don't make light of it. If this does not dim the enthusiasm for the vaccine in general and the role that it can play, but the safety issue is the big, overriding one for us.

I'd like to start on the other side of the room now, and take questions, two and three together and get a response from Dr. DuPont, and then we'll go around systematically again.

Do the data demonstrate overall efficacy of the vaccine for immunization of proposed target population? And then thirdly, do the data support greater vaccine efficacy against severe rotavirus gastroenteritis?

DR. DuPONT: I'll take them in reverse. The real, I think, important data that we've seen on efficacy is preventing severe rotavirus gastroenteritis, and that's the real value of this preparation. I think the efficacy on other, less dramatic, clinical expressions of disease are -- moderate is the word I would use.

I don't think they're terribly impressive, but I think the vaccine efficacy is solid for severe rotavirus gastroenteritis and I think that's what we

should be worried about. That's the condition that requires children to be seen by a doctor, requires their hospitalization, and is potentially fatal.

So I think that's not a limitation of the vaccine; it's just really putting it into perspective on where its real value is.

CHAIRPERSON FERRIERI: Thank you. Dr. Karzon, could you address these two questions please, and in the context of your response, a vote please.

DR. KARZON: The vaccine should do better than nature and this vaccine fulfills that criterion. It blunts severe disease; it does not blunt infection. In the sense it's the best of both worlds. And I think the blunting of severe disease is well demonstrated. Its overall efficacy therefore, is assured, giving a more benign mechanism of obtaining protection.

CHAIRPERSON FERRIERI: Thank you. Dr. Broome.

DR. BROOME: I would agree with the demonstration of efficacy for the severe gastroenteritis and the moderate efficacy against milder disease. I think it's important to think about how that is going to be perceived by the general population, because of course, there's a whole lot

more mild gastroenteritis than there is severe, and also may of these will not have specific etiologic diagnosis.

So I think there's a real communication issue in explaining to parents what can be expected from this vaccine and what cannot. And given my experience with only moderately efficacious vaccines, I think there's potential for some confusion.

CHAIRPERSON FERRIERI: I might add that this type of information will need to be communicated to physicians and primary care givers in order to translate the overall efficacy in weighing that against the goals of the vaccine. Ms. Cole.

MS. COLE: I agree with everything that's been said so far, and my vote is yes on, as far as efficacy against severe disease, and also moderate for the overall efficacy.

CHAIRPERSON FERRIERI: What is your off-the-cuff response, Rebecca, as a consumer to the issues of some of the reactogenicity data that we've heard and the acceptability as a parent and how others may respond?

MS. COLE: Well, I don't think any severe reaction to a vaccine is going to be taken well. I think they said there were what, 20 deaths in the

United States? No? Twenty hospitalizations, right? In the U.S. You're talking about worldwide though, over a million? Okay.

Well, they just have to make sure when they explain it to parents they do let them know that it can cause deaths. The numbers are not that large within the U.S. population, but they need to know that there is a possibility. Right, and it's worth preventing.

They are also going to be informed as to the care in which this is being given. You know, let them know we're not just giving them a vaccine that's going to cause severe fever and seizures; that that's being monitored.

CHAIRPERSON FERRIERI: Okay. Dr. Estes.

DR. ESTES: I think the data -- that this has good efficacy against severe gastroenteritis. It's very clear so I vote yes there. And it does have efficacy against -- for the proposed target population, although it's not as striking.

CHAIRPERSON FERRIERI: Dr. Hall.

DR. HALL: Dr. Fleming.

CHAIRPERSON FERRIERI: I'm sorry, Dr. Fleming. I didn't mean to overlook you; I was zoning out.

DR. FLEMING: My answer to question 2 is yes, and to 3 is yes, and I want to thank the investigators and sponsor and FDA for a very clear analyses and presentations, and important studies that have been done.

Having said that, a couple of additional points that to me are important in thinking about all this. The first is that I'm still a bit uncertain why there is the level of heterogeneity across trials that we see. I would agree with an earlier comment that the American Indian study seems to be quite consistent with the multicenter trial, but the Finn study looks quite different.

If we look at either the intent-to-treat or per protocol result on severe, the reduction is estimated to be 96 percent in the Finnish study and 65 and 81 in the two U.S. studies, and an odds ratio for 96 and over 65 is 13.

Interestingly though, the Finnish study, in addition to having the higher efficacy, has the apparent much greater concern with hospitalization for febrile illness. So there's almost a tradeoff there that seems to go hand-in-hand.

So I'm a little -- getting more insight into that inconsistency, and the inconsistency is also very

apparent when you look at the second season difference between the American Indian study and the Finnish trial; although I agree with Dr. Horn that we're probably getting a bias negative result against the vaccine in the American Indian trial.

But this heterogeneity is one of the concerns that I'd like to, at least try to better understand.

The other issue is, where is the benefits? And fortunately the benefit is where it matters the most, which is the severe illness setting. Dr. Rennels presented the results that showed that there is the reduction in RVGE over all levels, but those were nested analyses, and the essence of the benefit is really concentrated in the severe.

And if you just look at the study from the U.S., the multicenter U.S. study 312, by intention-to-treat analysis, there's 68 cases on RotaShield™ and 107 on placebo. Those break out in severe at 7 versus 35, and that's where the main signal is, that's where the main benefit is.

If you look at non-severe it's 61 versus 72. And so as I think Dr. DuPont had said earlier, in these non-severe cases there really doesn't seem to be substantial difference. And of course, also there's

not a substantial clinical relevance. The main difference is in the severe where it's 1.8 percent versus 9.1 percent -- or a seven percent reduction.

And coming back to my earlier comments about safety, that's the essence of what I understand we're really confident we're gaining, and we're putting that in the context of the appetite, irritability, activity reductions that are also on the order of seven percent.

When we look at the really important serious cases here, which would be hospitalization, there's only one or two in the 312 study. So we're talking about an order of a quarter-of-a-percent to a half-a-percent. And that's what I would put into context against the hospitalizations for febrile illness and the congenital anomalies: growth retardation and failure to thrive.

So bottom line is yes, I think these are studies that are clearly establishing efficacy, particularly where it matters in terms of severe disease, and yet it's very important since we're not talking about preventing polio or deaths or longer-term, more substantial, clinical parameters here, to be putting this benefit that's clearly defined in the context of what the safety is.

CHAIRPERSON FERRIERI: Thank you, Tom. Dr. Hall.

DR. HALL: For question 2 I will say yes, and for question 3, and I have no additional comments to what's been said.

CHAIRPERSON FERRIERI: Dr. Edwards.

DR. EDWARDS: Yes for 2; yes for 3.

CHAIRPERSON FERRIERI: Dr. Snider.

DR. SNIDER: With regard to question 2, moderate efficacy, against types 1 and 3 as what has been shown in the trials; is not to say that I don't think it would probably protect against 2 and 4 but we just have to acknowledge that it wasn't challenged -- the vaccine wasn't challenged.

And then thinking long-term, I just think we need to keep in mind -- I think there's -- in answer to 3, I think again, I agree with others; good efficacy. But I wonder what is going to happen if we protect the U.S. population against 1, 2, 3, and 4, if there's a niche then, for other serotypes.

And you know, that's just something we'll have to -- it's nothing against this particular vaccine; it's just something we need to be on the lookout for in the future.

CHAIRPERSON FERRIERI: My vote is yes for 2,

but support -- in agreement with just moderate efficacy -- and then yes for 3. And I'd like to reinforce the comment Dr. Fleming made regarding the heterogeneity of efficacy from one population to another.

I am concerned about what we may find -- the Finnish population is very genetically homogeneous and so this may relate also to some of the differences in immune response. So I'm a little bit concerned about going into third world countries that would be very genetically homogeneous in trying to predict what the efficacy and responses may be.

It may be again, rather unpredictable and there may be heterogeneity in efficacy that we're going to see in the populations in greatest need for protection against severe GE that have the highest death rates.

We move to question 4 and start -- I'm sorry, I missed Dr. Karzon. No, we've been voting on 2 and 3 comprehensively from the whole group, and so we've gone the full sweep and all of the people who have voted so far have voted yes on question 3, but -- absolutely on 3 -- and question 2 with support that it has moderate efficacy but not overwhelming. So we're all straight here. Claire.

DR. BROOME: I'd just like to clarify. I definitely vote yes on 3, but 70 to 80 percent efficacy is not outstanding efficacy. We're still going to see quite a few failures.

CHAIRPERSON FERRIERI: Yes, thank you, Claire, that's very important. It was the best against severe but not overwhelming, and that's a point that I think we all would be in agreement with.

Dr. Karzon.

DR. KARZON: You can't have 3 without 2.

CHAIRPERSON FERRIERI: I'm sorry, Nancy, I was trying to squeeze a few in together here, but we'll start on the other side of the room now. Dr. Snider, could you respond to question 4? And we will vote as you go down the line here.

Vaccine efficacy and its demonstration or not during a child's exposure to a second rotavirus season. Do you feel the data are adequate; do they demonstrate this efficacy for second season exposure?

DR. SNIDER: Well, as I recall the data, the best data were from the Finnish trial.

CHAIRPERSON FERRIERI: That is correct.

DR. SNIDER: And those data certainly were supportive of efficacy during the second season. The Native American data were much -- well, they really

didn't support it because the second season there wasn't much rotavirus infection.

And so I think the data are relatively limited. So my answer would be a qualified yes and that the data available do suggest it, but the data available are not overwhelming in terms of quantity of such data.

CHAIRPERSON FERRIERI: Dr. Edwards, how do you feel about this?

DR. EDWARDS: I think the data are inadequate to definitively answer this question and I would suggest that this be something that the manufacturer does continue to look at very closely. Because I think the Finnish data may not -- probably are not relevant, and probably that the American Indian data is not totally relevant for the whole population either. So I think -- I don't think I can answer yes to this, and more study I believe, is needed.

CHAIRPERSON FERRIERI: Thank you. Dr. Hall.

DR. HALL: I would agree with that, and I think some of the other factors that could contribute to that decrease, which seems to be at least immunity in the second season, needs to be further looked at.

CHAIRPERSON FERRIERI: Dr. Fleming.

DR. FLEMING: I think Dr. Horn is right about her concerns with being able to infer causality about the influence of the vaccine in altering the rate in the second season.

If you look in the American Indian trial where the results look very unfavorable in the second season, in the first season you're talking about roughly 60 cases out of 350 on the RotaShield™ and 100 cases out of 300.

In essence, if a case then induces particular protection for the next season, and if in fact there is, let's say a third of the cohort that's at particularly high risk -- i.e., not all individuals randomized are at equal risk -- then it's easy to envision that the second year around you're going to have a difference in the level of high risk or people who would have intrinsically been at higher risk who are still unprotected by not having had a case.

And if you see the same rate the second year, it doesn't mean the vaccine has completely lost its effectiveness. It's extremely -- you've lost your randomization, as Dr. Horn said, when you get into the second year.

So my answer to the question is in agreement. It's difficult for me to determine from

these data where there is protection the second year or not. The Finnish study and the American Indian study give very different-looking results. The Finnish study certainly looks very encouraging. The American Indian study doesn't, but there is this potential bias.

I'm more influenced by the overall results. Is this vaccine regimen giving you protection over the 2-year period; that is, those results are consistently positive-driven, in particular by the first year.

So answer to the second is, it's unclear but I'm not sure it's as compellingly important as the answer to the third question is.

CHAIRPERSON FERRIERI: Dr. Estes.

DR. ESTES: Well again, the data from the Finnish study I think, are very clear. I think the data for this country are not so clear so I would vote no for this country. We need more data.

CHAIRPERSON FERRIERI: Thank you. Ms. Cole.

MS. COLE: I agree.

CHAIRPERSON FERRIERI: Dr. Broome.

DR. BROOME: Although there's certainly a significant protection in Finland, it does look like the numbers are fairly small. So even there I think, it will definitely be important to look at the

experience in the future.

I guess I would say it certainly doesn't appear that there's any, you now, diminution of protection for that second season.

CHAIRPERSON FERRIERI: Well there may be, but we don't know. Dr. Karzon.

DR. KARZON: The data look as if there's some value in protection in the second year shown by Finland and to a lesser extent in the United States. I don't think that the test -- I don't think the situation put the question to the test in the Native American because there was little disease in the second year.

Now however, it's very likely again, comparing it with nature, that this is going to be quite as effective as a natural disease, and I think there's a real possibility that its effectiveness will not last.

And so I think we're scheduled for a very close, continuous look at its long-term effectiveness -- second, third, fourth year. And find out whether a later dose has to be given. I think that's a real possibility.

CHAIRPERSON FERRIERI: Dr. DuPont.

DR. DuPONT: In looking at the heterogeneity

of the United States and comparing it with the situation in Finland, I think there are a host and there are climatologic differences which are profound. And I think the answer is, we don't know about the United States and we need to look for efficacy for second seasons, second exposure. We don't know.

CHAIRPERSON FERRIERI: And my on the record answer is the same. I would agree with some of the members of the committee the data are inadequate. We know that natural immunity wanes over time and so I don't know that I expect the vaccine to behave that much differently. Dr. Karzon's suggestion is a valid one of continuing to assess immunity over time.

Dr. DuPont, could you start the ball rolling on question 5? Do the data support co-administration of the rotavirus with other childhood vaccines given at two, four, and six months? Examples being oral polio virus, DTP, and Hib.

DR. DuPONT: That's for me?

CHAIRPERSON FERRIERI: Yes.

DR. DuPONT: I think for the vaccines that were employed, and I believe those were the ones that were, that there is good support for co-administration of RotaShield™ with these routine childhood immunizations or vaccines. And I would be very

supportive of using them that way.

There are a number of vaccines which may be employed with the vaccine for which we have no data. But for these, it looks fairly solid, I think.

CHAIRPERSON FERRIERI: Thank you. Dr. Karzon.

DR. KARZON: I agree entirely. I feel safe in using surrogate markers for OPV, DTP, and Hib to indicate that there again, OPV has not been adversely affected. We are going to have to look at the other DTP conjugate and ask the same question. I think every time we go to a negative scheduled question should be addressed, and as I indicated at the outset, it's special.

We will similarly have to question whether we will alter the text in the elementary track of these new vaccines. And without certain numbers we may have to repeat some experiments if it gets to that desperate point.

CHAIRPERSON FERRIERI: Thank you. Dr. Broome.

DR. BROOME: I think there were a reasonably large number of children studied for the compatibility, and the results are generally satisfactory. The overall titer seemed a little low

for the Hib, but they're low in both groups and not very low, so I think they've demonstrated compatibility.

CHAIRPERSON FERRIERI: Ms. Cole.

MS. COLE: Yes.

CHAIRPERSON FERRIERI: Dr. Estes.

DR. ESTES: I would say yes. I think the data for the OPV in this country is good. It's not as clear for me for developing countries with the OPV that there's sufficient data to say yes.

CHAIRPERSON FERRIERI: Dr. Fleming.

DR. FLEMING: I have two concerns. One is with Pertussis. It seems to me that we would have to rely antibody surrogates that haven't been validated. So it's not clear to me on what basis we really can feel comfortable that we're truly not altering the efficacy.

And the other is for RotaShield™ itself. It's not clear to me from these data that we can say when delivering RotaShield™ in conjunction with DTP or the polio vaccine, that RotaShield™'s efficacy won't be altered. We simply, based on all the discussion today, can't rely on antibody levels.

So to my way of thinking it's not yet established in combination whether what we've seen for

efficacy of the RotaShield™ vaccine would be maintained.

CHAIRPERSON FERRIERI: Thank you. Dr. Edwards.

DR. EDWARDS: I think the data that's presented suggests that there's not interference, but I think that we're not using the vaccines that are the preferred vaccines currently, for the use of immunization of young infants. And certainly acellular Pertussis vaccine needs to be studied -- hopefully it's being studied already -- as well as IPV and Hib. So that even though these vaccines don't look like there's interference, I think that we are beginning to move away from at least two of these vaccines and other studies need to be done.

CHAIRPERSON FERRIERI: Good points. Dr. Snider.

DR. SNIDER: My answer would be yes, with the same caveats. That is, the decreased -- potential for decreased efficacy of the rotavirus vaccine, the concern about developing countries with OPV, the issue of Pertussis and the DTaP, IPV issues.

CHAIRPERSON FERRIERI: And my answer is yes regarding the data as presented.

Dr. Carbone, can we move on then to the

discussion points that are indicated on the second sheet? Thank you, Laraine. We touched on question 4, or -- we'll call these items -- item 4. I'll lead off on that.

We saw little data on safety in infants born prematurely. I think that we need larger numbers in order to respond more definitively. There were 70 premature infants who may have received the vaccine as I understand what Dr. Camardo presented at the very end there.

Are there other responses from the panel on that item? Kathy.

DR. EDWARDS: I think that one of the issues with prematurity also -- and probably Mary could address this better than I -- but just the tropism of whether this virus actually causes infectivity in the gut of a premature or what the differences are. Or also the whole role of maternal antibody or the lack thereof, I think, are things that clearly need to be looked at, and I don't think that have been adequately addressed with 70 patients.

CHAIRPERSON FERRIERI: Any other comments on this item? We've addressed item 1 in my opinion, Laraine. We didn't mention Hepatitis B but that's implicit in our needing encouraging further data that

would come forward on IPV, DTaP, as well as Hepatitis B and any other wild conjugates of all of the above.

What about the breastfed infant? Do you feel that we have any efficacy data on that? How does the panel respond to that? Would you like it to be defined very critically in the controlled way? Mary -- Dr. Estes.

DR. ESTES: I thought that -- at least in the studies in Finland -- these vaccines were given -- most of the mothers are breastfeeding and there was no -- the mothers were not told to stop breastfeeding. I think that my understanding of most of the data is that in fact, this vaccine works quite well in breastfed infants. At least where it has been studied.

CHAIRPERSON FERRIERI: Laraine, did you want more clarification of that point? Did you feel the data that were available to you were inadequate? I saw one or two analyses. I agree with you, Mary, but I don't remember such data from the American population. Was there also such? Do you want to address that point, Dr. Carbone?

DR. CARBONE: Just briefly to mention that the data we had from the American studies at the proposed dose were post-hoc type analysis and

relatively small numbers, and the definition of some breastfeeding versus none versus full-time, were difficult questions to answer. I would be interested in hearing the sponsor's response.

DR. CAMARDO: There was no difference in efficacy when we looked at breastfeeding in the U.S. study. As I said, we didn't -- I mean, in a way we lost our randomization there because we didn't have -- we didn't randomize to breastfeed and then stratify -- randomize and stratify to the group.

But when we did the post-hoc analysis there's just no difference. So you know, we don't feel like there's any interference with the vaccine.

DR. KARZON: What does the data show? How many cases?

DR. CAMARDO: It's right up here. There are 130 -- this is the whole cohort -- 130 with some breastfeeding; 268 with no breastfeeding; in the RotaShield™, 119 and 266. And 19 percent incidence of disease in the RotaShield™ group breastfed, versus 34 percent in placebo, and a ten percent incidence in the non-breastfed group versus 21 percent in placebo. So they're consistent.

The only -- there's a difference between the breastfed and non-breastfed groups in the incidence of

rotavirus disease. Which, I've discussed this at length with Dr. Rennels and this may be actually an artifact of reporting and you should remember we're not looking at actual disease but the reported disease. And then the stool collection and everything else.

But in a way it's reassuring that despite a fluctuation in the incidence of the disease in the subgroup, the vaccine is still efficacious in this study.

DR. SNIDER: What is the definition of, what would be the minimum for some breastfeeding? One day, one week?

DR. CAMARDO: The minimum is that the physician and the study coordinator confirmed that the mother was breastfeeding at dose 1. And I don't think it's a stretch to assume that some breastfeeding meant there was a reasonable amount during the dosing period -- which is actually pretty short. But we did not track in this study, days and confirm it. We just did not.

MR. HENCHAL: Really, what I think we were after here is -- this is Laraine Henchal -- is whether the committee would agree that this is adequate. There were some studies done to look at breastfeeding

interference done with a lower dose, and those didn't appear to have interference with breastfeeding. But this is all we have at this dose.

CHAIRPERSON FERRIERI: What do you think, Tom?

DR. FLEMING: Just one quick question. It would appear from these data that breastfeeding is not an effect modifier, but it does appear to be a predictor -- or just to look at it another way, if you look within the placebo rate, why is there, just within the placebo group, so much higher rate amongst those breastfeeding than not breastfeeding?

DR. CAMARDO: Good question. I don't know the answer. It's possible that it's related to reporting and not to anything else because we've -- I don't want to make a pejorative kind of a statement here -- but we sort of believe that maybe the mothers who are breastfeeding just had a chance to catch more of the cases and report them. I just can't tell you the answer, but that's one possible explanation.

CHAIRPERSON FERRIERI: I feel that it leaves it in limbo though, Dr. Camardo; that that answer isn't adequate.

DR. CAMARDO: You mean the answer --

CHAIRPERSON FERRIERI: It isn't for me; let

me qualify that.

DR. RENNELS: Let me just try. I can tell you, at least from my sites, that it's the higher socio-economic groups who breastfeed and I can tell you also that it was the suburban high socio-economic groups who reported more episodes of gastroenteritis than did the site of lower socio-economic.

And I think that's the explanation but I can't prove it beyond my sites.

CHAIRPERSON FERRIERI: Thank you. Other responses on this issue from the panel? Yes, Ms. Cole.

MS. COLE: Wasn't there a report recently that it was advised that women breastfeed a baby up until age one year? Then we're probably going to see an increase in breastfeeding and for longer periods of time. So I think this is something that's very, very important to be looked at since all those babies are immunized all under one year.

CHAIRPERSON FERRIERI: You're correct that someone who's closer to the Academy than I, that there are recommendations that breastfeeding through the first year of life is recommended. Yes.

DR. MALDONADO: Should I make a comment even though I can't -- I think there was a paper in either

this month's or last month's Pediatric Journal that looked at breastfeeding patterns among higher socio-economic status women, and in fact, women obviously are in the workforce now.

And what was found was that a very high percentage of higher socio-economic status women were breastfeeding at delivery but by four months it had dropped substantially, and by six months almost 100 percent had stopped breastfeeding.

So in fact, the breastfeeding rate may drop over time because in fact, that data suggests that breastfeeding is not protective, and we have seen other data that seem to show that breastfeeding should be protective.

MS. COLE: Excuse me. Was that study done -- was that released before or after the recommendation that women breastfeed until age one? Because you're saying there's going to be a decline --

DR. MALDONADO: The recommendation was just released about a week ago, and this is an older study, right, and so --

MS. COLE: So it's possible we're going to see an increase, not a decrease.

DR. MALDONADO: It's hard to say because in fact, these were women who were working and really --

again, the issue was made in the paper that efforts to make it easier for women to breastfeed while they're working should be made. So we don't -- I mean, I don't know.

CHAIRPERSON FERRIERI: Well, for Bangladesh, India, Africa, and other parts of the world where deaths are very high, breastfeeding rates are quite different and unpredictable at times, depending on the pressures from suppliers of formula. Claire.

DR. BROOME: I think it's important that we separate out what the study can tell us and what it can't. It's not designed to look at the risk of breastfeeding and risk of rotavirus disease. So I don't think it's really -- you know, it's very interesting to look at this difference in attack rate, but there really isn't anything you can tell from this data.

What you can tell is, it's a randomized study to look at vaccine efficacy. And this analysis stratifies by whether the women were breastfeeding or not. And in addition to the overall efficacy you also see efficacy in both the subgroups which is of a comparable order of magnitude to the overall.

So you know, I'm reasonably satisfied that breastfeeding status is not going to affect the

performance of the vaccine in this population.

CHAIRPERSON FERRIERI: In which population?

DR. BROOME: This is the U.S. multicenter trial.

CHAIRPERSON FERRIERI: Does anyone want to attack question 3, safety for vaccination of children in contact with immunocompromised hosts? Yes, Dr. Modlin.

DR. MODLIN: This is a very interesting conundrum, I think, in that all of the children in these trials -- in all of these trials children were excluded if they were in households in which there was -- "an immunocompromised individual" was located.

And one of the questions I didn't get to ask earlier this morning was what actually defined an immunocompromised person in the household? So maybe if someone from the company could clarify that then maybe we could go on from there, because there are two or three rather important issues.

DR. ZITO: Ed Zito from Wyeth. It was just by asking the parent whether or not someone was receiving immunosuppressive therapy, on systemic steroids. And that was pretty much it.

CHAIRPERSON FERRIERI: Someone who had received --

DR. ZITO: Someone who was identified as --

CHAIRPERSON FERRIERI: Yes, cancer, leukemia, post-organ transplant, HIV. Yes. All of the above.

DR. ZITO: Yes.

CHAIRPERSON FERRIERI: The usual groups, John.

DR. ZITO: But there was no specific testing to identify. But that's the case and we don't have any data to address the issue because children were excluded. I guess -- therefore, unfortunately I think, the FDA is going to have to rely on opinion -- whether expert opinion or not is another issue.

To the best of my knowledge, there have only been one, perhaps two papers in the literature that have addressed the issue of severity of rotavirus disease in the immunocompromised patients.

There was a paper from Hopkins in the early '80s -- Bob Yokum and Tim Towson were authors -- indicated that there was -- Dr. Greenberg was involved -- where there were -- showed that in the bone marrow transplant unit there, there was an outbreak of rotavirus disease and there was considerable morbidity, and I believe some mortality -- although granted, we'd have to go back and check on that.

I'm not aware of any other information that rotavirus represents a risk to anyone who's immunocompromised otherwise. And I guess this would be the appropriate forum to raise the issue. And I think we probably ought to start by asking the experts, the real experts in the room if they're aware of any other information.

CHAIRPERSON FERRIERI: Anyone on the panel?

DR. ESTES: Well, there certainly is data in immunocompromised children who get wild type rotavirus infections, that many of those children will excrete -- become sort of persistently infected. They'll excrete virus for a long, long time. That is known, but I don't think their disease is any more severe than the disease in a normal child, except that they don't clear the virus.

CHAIRPERSON FERRIERI: That was my impression from our bone marrow transplanted patients. I'm concerned about it. Some of them have graft versus host disease and have gut involvement as part of their GVH. But even those who do, I don't know anyone in our institution over the years who has died from disease due to rotavirus. But they have shed it a long time, just as they shed adenovirus in their stools and other things.

Dr. Edwards, did you want to add to that?

DR. EDWARDS: Well, I think Dr. Kapikian's discussion does make me a little concerned that maybe the vaccine strain may spread quite widely. And so I think that certainly is information that we need I think, more of in terms of normal children and their excretion to other individuals.

CHAIRPERSON FERRIERI: If you are vaccinating someone within a household with an immunocompromised host there, the likelihood of transmission would be quite good based on the data. I don't know if Dr. Kapikian is nodding his head there, but I don't know how far FDA would like to go on it but I think we do need to know more.

DR. MODLIN: You can extend the argument, the obvious argument that naturally occurring virus represents a greater risk to the immunocompromised household contact than does vaccine virus.

And therefore, even in the absence of data, I guess this is almost more of an issue to a certain degree, for the advisory committees, but on the other hand -- well, it's a major issue for the labeling as well. And I guess I would -- the next thing I'd like to do is ask the FDA about their opinion about including something like this in the label in the

absence of any information from the existing trials.

CHAIRPERSON FERRIERI: Yes. Before they respond I'd like -- Dr. Broome, you had your hand up perhaps?

DR. BROOME: I just wanted to second your suggestion earlier that the FDA look at what we know about the circulation of vaccine strains in the placebo group from the Venezuelan trial.

CHAIRPERSON FERRIERI: I think we're in agreement. But how would FDA, in response to Dr. Modlin -- what would suffice at this point -- "information on the responses of vaccine virus to compromised hosts is unknown". You would consider putting in something that makes no claims?

DR. CARBONE: We've had some very similar thought processes here that, the obvious argument is that the vaccine is less pathogenic than the natural disease and that may -- and since the immunocompromised person as is the child, likely to be exposed to the wild type virus, that perhaps this was an improvement.

And if you could reduce -- you at least wouldn't be exposing them to anything more pathogenic than they're going to get exposed to anyway. But of course the vaccine doesn't have evidence of preventing

excretion of the wild type, so that argument may not be as valid.

I agree the issues of the studies in Venezuela and the circulation of the vaccine strains are important because until we can find out whether the children actually excrete vaccine virus, say measured sequentially for a longer time than wild type, that would become an important information about the ability of this virus to persist in the normal host versus the immunocompromised host.

But I think the bottom line is, from a label issue, at the current state we don't have the information on the children who are associated with immunocompromised hosts and we're currently in discussions as to how that should be reflected in the label without additional data. It's a concern of ours as you can tell by us putting it on this list.

MS. COLE: Excuse me.

CHAIRPERSON FERRIERI: Yes, Ms. Cole.

MS. COLE: Could you -- as far as the label goes -- just let the public know, and physicians know of course; I know there's a part for each one on labels -- that even though there's no data that, is there some recommendation you could give them of what action to take should this occur?

DR. CARBONE: Well, that's the difficulty. We can tell them on say, the package insert, what data we have and do not have to support this. What to actually recommend is actually a quandary for us because people were excluded from the study and we don't know what the effect is on contacts.

DR. SNIDER: Don't you think it would say something like the safety is unknown? That the physician should weigh the risk of the vaccine versus the natural infection, blah, blah, blah?

CHAIRPERSON FERRIERI: Exactly.

DR. CARBONE: It's hard to make any kind of definitive recommendation without the information.

CHAIRPERSON FERRIERI: Well, I'm afraid we have to call the meeting to a close. I want to thank everyone for their participation. We're going to have the availability of throwing our material in this bin here, if you will. Anything written that's confidential Nancy, you would like back? The data from the sponsors should stay here.

DR. FLEMING: Patricia, could I make just one brief, additional comment?

CHAIRPERSON FERRIERI: What is it?

DR. FLEMING: Shouldn't be more than ten minutes. Just a quick thought relative to the more

than 30-week cohort.

Specifically, we have made recommendations that I'm very comfortable with that relate to the aggregate group, and Dr. Halsey, in fact, had made the point that there are concerns with an approval that would be restricted. And as a statistician I'm particularly comfortable with the perspective that we really ought to be putting the essence of our perspective on approvals on the entire cohort.

But if in fact, risk benefit is judged to be adequate for marketing, I would encourage that special attention be given in surveillance to looking at this cohort. When we heard from Dr. Glass up front, one of the major -- his argument of one of the major clinical issues in this setting are the hospitalization rates that can occur with up to one percent frequency.

And we've seen in these data indications of febrile illness as well as some of these other phenomenon such as congenital anomalies, growth retardation, failure to thrive, that are focused particularly in this group.

And I would argue that if broad marketing occurs that there be particular efforts made in surveillance to assess whether the rates of these occurrences are not in excess of the levels of benefit

that we hope to achieve of the most serious nature, which are on the nature of one percent.

Thank you.

(Whereupon, the Advisory Committee was adjourned at 3:36 p.m.)